THE NEUROPSYCHOLOGY OF SCHIZOPHRENIA, SYMPTOMS AND MEDICATION

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DECLARATION

I, Andrew Rogers, declare that the work contained in this thesis is my own.

Signed....

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CONTENTS

ABSTRACT

This thesis attempted to investigate the relationship between symptom expression, medication effects, outcome status and neuropsychological functioning in schizophrenia. As the heterogeneity of schizophrenia is now widely accepted, symptom ratings from the comprehensive Positive and Negative Syndrome Scale (Kay et al., 1986) were entered in to a factor analysis after the work of Liddle (1987) and Liddle and Barnes (1990). The factor analysis of symptoms was carried out with patients at both the acute stage of illness and at the chronic stage. Almost twice as many chronic patient subjects were used in the latter study than had been used before (n=66). The acute stage analysis was seen as a preliminary investigation as only twenty six patients were recruited. This reflects the difficulty in recruiting early stage floridly ill patients for demanding psychiatric and neuropsychological assessment. The emergent factors, at each stage, were correlated with neuropsychological performance on an array of executive, memory, psychomotor and hemispatial neglect tests. Neuropsychological assessment was also compared with healthy control data to assess the degree, if any, of impairment from the norm, independent of symptoms. In the chronic stage study, four factors coined reality distortion, poverty of sociability and affect, disorganisation and excitability were generated. Poverty of sociability and affect was related to impaired short term working memory, episodic memory and semantic verbal fluency. Disorganisation significantly correlated with episodic memory functioning and disinhibition of inappropriate responding. None of the other factors were directly related to neuropsychological performance. The relation

between episodic memory functioning and poverty of sociability and affect was explained in terms of poor cognition due to developmental experience and the retention and use of socially appropriate schema. Disorganisation appeared to be underpinned by possible frontal type organisational difficulties in the correct temporal ordering of information for recall. At the acute stage, five factors emerged reflecting a paranoid state, poverty of affect, disorganisation/poverty of sociability and delusions. None of these factors or sub syndromes was significantly related to neuropsychological functioning possibly due to the instability of symptom expression, at this stage, invalidating the sub syndromes as reliable indicators of sub pathologies. Both chronic and acute patient groups were impaired on executive, memory and psychomotor functioning compared to normals. The sub syndromes expressing abnormal experiential behaviour were considered to be products of cognitive biasing in social relations underpinned by gross neuropsychological deficits.

No clinical or neuropsychological benefit was seen during a controlled drug trial involving high doses of chlorpromazine and the atypical neuroleptic, risperidone, and standard drug regimes with historically treatment resistant patients. Neuropsychological deficits (and clinical status) may be enduring phenomena of this type of patient and were proposed as responsible for most of the social and vocational impairment that characterises treatment resistant chronic schizophrenia. In an attempt to investigate the particular neuropsychological correlates of poor outcome or treatment resistant schizophrenia, episodic memory dysfunction was highlighted as characterising poor outcome functioning. Executive impairments, from initial analysis, became non

discriminatory of poor outcome after controlling for education background. The marked differences in education background between good and poor outcome groups supported previous research that suggests early and insidious onset of illness characterises poor prognosis (Lieberman and Sobel, 1993). The insidious nature of the illness process, in poor outcome, with poor episodic memory, might lend support for a neurodevelopmental impoverishment and retention of appropriate social knowledge that manifests itself as poor social functioning in adult relations. The implications of the poor episodic memory functioning and its relation to social disability is discussed with reference to therapeutic strategies for this type of schizophrenic patient.

THE NEUROPSYCHOLOGY OF SCHIZOPHRENIA, SYMPTOMS AND TREATMENT RESPONSE

CHAPTER 1

INTRODUCTION

1.1 Schizophrenia-the History of the concept; Definitions and Types.

Schizophrenia has been coined the 'heartland of psychiatry' (Kendell, 1986) and persists at the epicentre of clinical practice. It is an extremely complex and disruptive illness affecting, on average, 5 out of every 1000 adults (Hamilton, 1984; Warner, 1985) and many more, indirectly in the form of family, friends and colleagues. Schizophrenia is also a concept that has been shrouded in controversy for most of the hundred years of its existence. In fact, hypotheses have been proposed to account for schizophrenic breakdowns implicating nearly every variable known to effect human behaviour (Bentall et al., 1988). The purpose of this thesis is to provide an account of schizophrenic behaviour in terms of cognitive neuropsychology. That is to provide a description of the information processes that underlie specific areas of schizophrenic behaviour. Many of the controversies surrounding the concept will be dealt with in pursuing this explanation. However, primarily the thrust of the following studies is to investigate those possible neuropsychological functions that, when impaired may singularly or in concert, give rise to behavioural phenomena characteristic of a recognised schizophrenic illness. This thesis will also deal with an examination of the relationship between schizophrenic symptoms,

neuropsychological functioning and medication used to ameliorate the disorder. Finally, there will be an examination of the relationship between the neuropsychological functioning of schizophrenic patients and treatment response to uncover any possible cognitive correlates of good and poor outcome.

1.1.2 The History of the concept

Emil Kraepelin in the fifth (1896) edition of his 'Lehrbruch' is commonly credited with the first unambiguous classification of insanity, to date, encompassing that form of disease we now refer to as schizophrenia.

Kraepelin divided mental illness into 'manic depressive insanity' and 'dementia praecox' and described them in terms of their long term course. He believed that dementia praecox was a progressive disease which gradually lead to either chronic invalidism or only partial recovery, if any improvement arose at all. The term 'dementia praecox' described the characteristic early onset of the disease and the ensuing intellectual deterioration. Among the major symptoms he described were hallucinations, delusions, negativism, attention difficulties, stereotypical behaviour and emotional dysfunction.

In 1911 Eugen Bleuler published his 'Dementia Praecox or the Group of Schizophrenias'. He tried to define the core nature of the disorder and to get away from the prognostic emphasis of Kraepelin. Although he sought to confirm and develop Kraepelin's original concept he, in fact, changed the idea of dementia praecox fundamentally. Eventually, his term 'schizophrenia' won universal acceptance as the overall label for the disease. He chose this 'split mind' concept since his direction was psychological rather than

neuropathological. He believed that the core nature of schizophrenia comprised of a 'loosening of associations' in thoughts, speech, emotions, volitional acts and cognitive acts in general. He differed from Kraepelin on two major points. Firstly, he believed there was no necessary early onset and, secondly, there was no inevitable progress to dementia. Psychoanalytical theory had a major influence on Bleuler's theorising and it appeared he was trying to provide for the psychoses what Freud had done in specifying the underlying psychological processes responsible for neurotic behaviour.

Kraepelin's descriptions were seen as narrow and limited diagnoses to patients with poor prognosis; he dismissed those patients with good outcomes as unrepresentative of 'real' dementia praecox and were rather representative of another category of illness. Bleuler's concept was broader and possessed more theoretical emphasis. He embraced those patients with good prognoses and added those whom, he believed possessed 'latent' schizophrenia in his group of schizophrenias.

Bleuler's greatest influence was in the U.S. where his proposed 'primary' symptoms (loosening of associations-or thought disorder-, blunting of affect, autism and ambivalence) were used as the basis for diagnosis whether hallucinations were present or not (Kendell, 1986). These criteria became so widely used that the concept nearly embraced the whole of severe mental illness. For instance, its influence can be checked by the percentage diagnoses of schizophrenia at the New York Psychiatric Institute in the 1930s compared to the 1950s. In the 1930s 20% of patients were diagnosed schizophrenic compared to a peak of 80% in 1952 (Davison and Neale, 1986).

The concept was additionally broadened by subtyping. Kasanin (1933) observed symptoms in a group of patients, originally diagnosed as 'dementia praecox', as a hybrid of schizophrenic and affective characteristics, suggesting 'schizoaffective psychosis' as an appropriate label. This concept was listed, along with the aforementioned diagnoses, in the Diagnostic and Statistical Manual of Mental disorders I (American Psychiatric Association, 1952) and DSM II (APA, 1968).

In the 1960s and 70s a 'process-reaction' philosophy was embraced; 'process' for the indication of the basic physiological brain malfunction (involved in insidiously developing schizophrenia) and 'reactive' due to a stress component (Davison and Neale, 1986). This philosophy held sway for the ensuing direction of investigation.

Of great influence in the conceptualisation of schizophrenia were those symptoms collectively defined by Schneider (1959). These 'First Rank Symptoms' were based on an appraisal of the acute stage of the illness. The symptoms in question consisted of auditory hallucinations (ie. discussing the subject in the third person, running a commentary on the subject's thoughts or behaviour), thought insertion or withdrawal, thought broadcasting, the sensation of actions being controlled externally, passive and reluctant recipient of sensations from an external agency and delusional perception. Schneider considered these symptoms as convenient diagnostic aids. However, he accepted that patients with otherwise typical schizophrenia may exhibit few or none of them. In spite of this, he felt that such symptoms were worth distinguishing from so called 'Second Rank Symptoms' eg. perplexity, emotional blunting and hallucinations and delusions of other kinds.

1.1.3 Definitions and Diagnosis.

Schizophrenia is defined by those symptoms or groups of symptoms which characterise the disorder and which discriminate it from other forms of mental illness. Problems arise when considering which symptoms are the most discriminating and which symptoms are the most emphatic. Cooper et al (1972) showed a major discrepancy between diagnoses of manic depression and schizophrenia when comparing U.S. and English psychiatrists. There was twice the incidence of diagnosis of schizophrenia in New York institutions as in London. In the International Pilot Study of Schizophrenia (World Health Organisation, 1973) psychiatrists in Washington and Moscow were seen to use a significantly broader concept of schizophrenia for diagnosis than their counterparts in any of the other seven international centres studied. Such low reliability necessitated a review of criteria so that an operational definition could be established for universal clarification and use. A definition was sought in line with the presence of particular symptoms or combination of symptoms, by the course of the disease or via a combination of the two. The ideal was to choose a definition useful in predicting response to treatment or long term course, or how disease expression corresponds most closely with any putative underlying biological abnormality-however, there is, as yet, no clear agreement concerning this. It is becoming increasingly apparent that insidious onset is associated with poor prognosis (Lieberman and Sobel, 1993).

Currently, the most widely used definitions are American and have key elements in common:

1) The St. Louis Criteria (Feighner et al, 1972) which stipulates the patient as ill, not necessarily psychotic, for at least 6 months. Any sign of manic depression or mania

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1) The St. Louis Criteria (Feighner et al, 1972) which stipulates the patient as ill, not necessarily psychotic, for at least 6 months. Any sign of manic depression or mania

symptoms excludes the patient from diagnosis. The only psychotic symptoms required are hallucinations and delusions of any type or clear cut signs of thought disorder.

2) The Research Diagnostic Criteria (RDC) (Spitzer et al, 1978). This allows a definition in 'broad and 'narrow' terms dependent on the number of symptoms present from a specified list. The RDC requires a two week duration of symptoms in the manner of thought disorder, hallucinations and delusions of particular (usually Schneiderian) kinds and that no affective symptoms are present simultaneously.

3) The Diagnostic and Statistical Manual of Mental Disorders (3rd. edition; American Psychiatric Association (APA), 1980- revised APA, 1987). This requires onset before 45 years of age and that signs of illness be present for at least 6 months. If these are not fulfilled the diagnosis is usually one of 'schizophreniform' psychosis. A diagnosis involves the presence of at least two of the following: delusions, prominent hallucinations, incoherence, catatonic behaviour and flat or grossly inappropriate affect. The DSM IV (APA, 1994) diagnostic criteria for schizophrenia has recently been published but differs little from the DSM III-R diagnosis. Both these diagnoses highlight social/occupational dysfunction, the exclusion of schizoaffective and mood disordered patients from diagnosis along with those patients whose disturbance is directly associated with drug abuse/medication or is part of a general medical condition. For those patients with a developmental disorder such as Autism, an additional diagnosis of schizophrenia is only made if prominent delusions/hallucinations are present.

Other classifications include the 'flexible' criteria of Carpenter et al (1973) which uses ratings from the Present State Examination (Wing et al, 1974). The 'flexible' system allows a 'broad' (5+ items) or 'narrow' (6+ items) diagnosis. The CATEGO classification system (Wing et al, 1974; Wing and Stuart, 1978) is a computer programme which

processes data from the PSE (or the associated symptom checklist). Nuclear symptoms carry the most weight and CATEGO is seen as faithfully Schneiderian.

The benefit of comparability of systems for accurate diagnosis may cause confusion for practitioners when faced with a patient whose symptoms do not fit comfortably into one of the available systems. A remedy could be available with the advent of the International Classification of Diseases (10) which provides two sets of definitions, one purely descriptive for clinical purposes the other of an operational format for research.

1.1.4 The Signs and Symptoms of Illness

In its acute form schizophrenic onset occurs most commonly during adolescence or early adulthood, often developing insidiously. Delusions are variable in form but are often persecutory, grandiose or religious. They are experienced as passive phenomena ie. there is little control of one's own thoughts, feelings or will and thought insertion, withdrawal and broadcasting are also commonly perceived. The subjective interpretation of these phenomena lie beyond normal experience and also appear culturally dependent. Auditory hallucinations (voices in the second or third person i.e. either keeping a commentary on the patient's behaviour or conversing about them), again, are common as are sensations of perplexity. General flattening of affective response and incongruous/inappropriate behaviour is also a particularly common abnormality at this stage of the illness (Kendell, 1986).

In chronic illness more episodes are experienced more insidiously and last longer. This 'defect state' is less conspicuous than the florid symptoms that characterise the acute case. A patient's drive and determination is weakened, there is a loss of interest in others, a reduction in speech and the capacity to form enduring relationships is reduced. Most patients in the chronic stage do experience recurrent episodes with delusions and hallucinations; depression is also a common feature. Many schizophrenics do appreciate this situation as desperate and 10% die by suicide in the early years of their illness (Miles, 1977).

From the original division of symptoms into positive(abnormal experiences) and negative(poverty of functioning) clusters by Hughlings-Jackson in the 19th century, Crow

(1980) has attempted to encapsulate the underlying pathology of acute and chronic, positive and negative symptoms into a new subtyping system. He coined the term 'type 1' schizophrenia as characteristic of traditional positive symptomatology and encompasses delusions, hallucinations and thought disorder. 'Type 2' schizophrenia encompasses mainly negative symptomatology including flattened affect, apathy and poverty of speech. Crow (1980; 1985) argued that type 1 is particularly responsive to neuroleptics while type 2 is not. The purpose of this subtyping was to reflect the differing pathological pathways of the clusters of symptoms expressed. Type 1, the author suggested, is associated with dopamine transmission dysfunction in the mesolimbic system. Type 2 is associated with cognitive impairment and structural changes in the brain. Andreasen (1991) noted that positive symptoms tend to correlate well with each other and not with the negative (and vice versa). Generally, positive symptoms tend to characterise the acute phase of the illness, negative the chronic. However, both can often co-exist in the same patient.

1.1.5 Epidemiology

In most industrialised western European and North American countries the lifetime risk for schizophrenia is approximately 0.5-2%, with about 15-30 new cases per 100,000 of the population per year (Kendell, 1986; Bebbington and Mc Guffin, 1988). The International Pilot Study of Schizophrenia (WHO, 1973) recorded substantial numbers of schizophrenics in all the countries involved despite widely differing languages, religion, culture and degree of urbanisation. Sartorius et al (1986) noted that schizophrenics in all of these centres displayed remarkably similar core symptoms suggesting that schizophrenia is a fairly stable illness across a wide range of cultures and ethnic groups.

The age of onset, for schizophrenia, is usually between the ages of 15 and 45, often a few years earlier in males than females, on average (Kendell, 1986). Generally, there is agreement that schizophrenics have a raised mortality (shared with other forms of mental illness) and also raised morbidity (Baldwin, 1979).

The season one is born in has also been noted as possessing some aetiological significance. In Norway, Sweden, Denmark, England and Wales schizophrenics are more likely to be born in the first 3 months of the year than the rest of the population and less likely to be born in the months July to September. In Australia this pattern is reversed reflecting seasonal reverse (Watson et al, 1982). This seasonal variable may be a consequence of an infective agent or diet acting either in utero or in the early months of life.

1.1.6 Criticism of the concept.

Recent years have seen an increasing body of psychiatrists and psychologists challenging the nature of the schizophrenia concept itself (eg Bentall et al, 1988) or, at least, there has been a questioning of the strict 'medical model' closely adhered to by clinicians and researchers alike over the last century or so. More social (Scheff, 1966) or psychological (Laing, 1967) models have been proposed to account for the entity understood as schizophrenia. Such theories have come to light as the literature seems to have consistently failed to find the single essential biological substrate schizophrenia necessitates as a disease entity (Szasz, 1961). Richard Bentall (1988) argued that no substantial progress has occurred in over a century of research into schizophrenia as a

unitary concept. This, he argued, is due to schizophrenia not fulfilling the criteria of a meaningful scientific concept-its status as a syndromic disease is undermined by a lack of an agreed biological basis and that diagnosis is a poor predictor of course, outcome or treatment response. Patients diagnosed as schizophrenic have been shown as exhibiting mutually exclusive symptomatology (Bannister, 1968) thus, two patients with the same diagnosis may exhibit completely different symptoms. Also, differential diagnosis from other psychiatric disorders presents an additional conceptual problem. In some follow up studies (of outcome) when first admissions are taken into account, many patients, initially, diagnosed schizophrenic were subsequently diagnosed as suffering from affective disorder on their second admission (Kendell et al, 1979). Strauss and Carpenter (1974, 1977) noted that symptoms on admission appear to be a poorer predictor of outcome than social and family (Vaughn and Leff, 1976).

Bentall et al (1988) concluded "..there would seem to be little reason to feel confident about the validity of schizophrenic diagnosis" (p.314). The authors criticised the dominant role of the medical profession in the management of psychosis and their continuing application of a biological approach concentrating on non-social drug oriented forms of therapy. Why the concept of schizophrenia, therefore, remains in common usage, clinically and in research, may be due to the professional interest of psychiatrists rather than the adherence to sound scientific method.

Researchers and clinicians, therefore, must be aware of the anomalies inherent in the concept as it stands. This being so, research and evaluation is not seen, by its critics, as redundant, rather classification requires a wider scope of opinion than is offered

presently. Bentall et al (1988) proposed that an abandoning of classification in favour of research into particular symptoms maybe more profitable. Other researchers prefer to concentrate on related clusters of symptoms as providing evidence for specific subpathologies of illness (Liddle, 1987) or explaining types of symptoms (abnormal experiences, poverty of action) in terms of different expressions of an underlying global impairment in consciousness (Frith, 1992). Although these approaches may forge a new appreciation of schizophrenic symptomatology and how they are psychologically mediated, they preclude neither an underlying biological basis nor an interaction between biology, psychology and social factors.

1.2 The Neuropsychology of Schizophrenia

The symptoms and signs of schizophrenia are behavioural phenomena. Crudely, positive symptoms express some form of abnormal beliefs and/or perceptions and negative symptoms demonstrate deficits in competent activities. However, some commentators would argue that the degree to which these behaviours can be judged as abnormal is debatable but would see them rather as normal reactions to abnormal experiences (e.g. Maher, 1974). Those who suffer these symptoms are experiencing, for the most part, disturbing psychological phenomena alien to most.

The turn of the century heralded a watershed in neuroscientists' understanding of the association between brain functioning and behaviour through the study of patterns of

deficits expressed by patients with neurological problems. Through the work of such notables as Broca (1861) and Wernicke (1874) psychological models of normal information processing emerged ascribing certain cognitive functions i.e. language (input and output processes) to particular areas of the brain. Alzheimer (1907) was able to show that certain intellectual deficits could be ascribed to particular qualitative and quantitative changes in the neural make up of the brain. Kraepelin thought that it would only be a matter of time before the functional deficits and behavioural phenomena associated with schizophrenia (dementia praecox) could be explained in similar neuropathological terms. Researchers since have been striving to fulfill Kraepelin's optimism in attributing schizophrenic symptomatology to some specific brain abnormality. However, it was not until the 1950s with the discovery of antipsychotic medication (chlorpromazine) that a focus for the consideration of schizophrenia as a brain disease was really found. The efficacy of this type of medication in ameliorating, at least, the positive aspects of the illness lead researchers to infer that underlying such symptoms was some form of abnormality in the activity of the neurotransmitter dopamine. Support for this view has come from animal studies where dopamine agonist administration was seen to model some of the behavioural aspects of schizophrenia (see McKinney and Moran, 1981), indeed behavioural sequelae of amphetamine ingestion in humans appear to reflect many of the core symptoms of schizophrenia (Angrist et al., 1974). Johnstone et al. (1978) showed that dopamine antagonism was essential for symptom amelioration. Despite this, Van Kammen et al. (1982) reported improvement in a significant proportion of

schizophrenic patients after amphetamine administration. A direct dopamine overactivity hypothesis has, thus, been seen as too simplistic an explanation of the underlying physiological abnormality associated with schizophrenic symptoms (Birchwood et al., 1989). Recent advances in biological assaying techniques have enabled neuroscientists to investigate the biochemistry and physiology of the brain in greater detail. However, the results of such studies have tended not to lend unequivocal support for theoretical positions such as the 'dopamine theory' rather they reveal quite a complex picture of brain physiology intimating that multiple neurotransmitter systems may work in concert with each other rather than as separate agents. To what degree these systems work together in controlling which functions is, as yet, not understood. Within the realm of schizophrenia research, the physiological abnormality underpinning particular symptoms has now extended to the investigation of several different neurotransmitter systems encompassing a range of monoamines (e.g. acetylcholine, serotonin and other types of dopamine systems), several aminoacids (e.g. GABA) and neuropeptides (e.g. opioid peptides such as beta-endorphins) whose dysfunction may be implicated, to differing degrees or acting together, in composing the biological substrate necessary for the formation of schizophrenic type symptoms. Thus an extremely complex field requires much more research to single out systems and combinations of neurotransmitter activity whose dysfunction may be implicated in the expression of schizophrenic symptoms. The physiological basis of schizophrenia, despite this evidence, also appears to be limited in as much that neuroleptic amelioration (of usually just positive symptoms) does not occur in

up to 30% of patients diagnosed as schizophrenic (Davis et al., 1980). Some patients whose symptoms tend to be characterised by a defict of functioning i.e. negative symptoms have been seen as less responsive to the pharmacological effects of standard neuroleptics on their conditions as opposed to more acute forms of illness which are characterised by positive symptomatology (Crow, 1980). Crow suggested that, based on this evidence, schizophrenia may result as the expression of more than a single pathological process. In this light, the negative aspects of the illness have been associated with some form of structural abnormality in the brain.This has been supported, in part, by recent advances in scanning technology that have shown increased neurodegeneration of brain tissue of schizophrenic patients compared to controls (Johnstone et al., 1976; Golden et al., 1980). However, such observations, as increased ventricle to brain ratio size, have been recorded in as few as 6% of cases of chronic schizophrenia (Andreasen, 1982) and not at all in a sample of young schizophrenic patients (Jernigen et al., 1982). However, even structural abnormalities reported tend not to resemble a chronic degenerative process but rather indicate that the abnormalities may result from some aberrant maturation process i.e. a neurodevelopmental disorder that expresses itself in behavioural terms at the end of the maturation process which would tie with most reports of the age of onset of the first episodes of schizophrenic behaviour (Weinberger, 1987).

In conclusion, attempts to single out a specific brain functional/structural abnormality implicated in the expression of schizophrenic symptoms have not produced encouraging

results. The picture is, however, complex and the results to date do not account for all those suffering the illness. Also, different abnormalities appear to be associated with different phases or clusters of symptoms attesting to possible differing pathological processes involved in the expression of the different forms of the illness. Such observations highlight the heterogeneous nature of the illness and should provide both caution and alternative routes of investigation in the clarification of a link between underlying putative brain abnormalities and schizophrenic symptoms.

Assuming some form of brain pathology is associated with specific dimensions of the illness, the purpose of this thesis is not to debate this subject at length but rather to acknowledge that the behaviours associated with schizophrenia may indeed have some underlying biological correlate. However, our aim is rather to examine the nature of schizophrenic symptoms as psychological phenomena i.e. to investigate the association between abnormal psychological functioning and abnormal behaviour. It seems necessary to state that it is inadequate to suggest that an abnormality of dopamine neurotransmission, for instance, is responsible for auditory hallucinations as such an explanation emphasises an association rather than causation of the behaviour. To examine the nature of the symptoms of schizophrenia, therefore, researchers are presently more wont to explain abnormalities whether physiological or psychological as separate 'levels of explanation' (Mortimer and McKenna, 1994) in an attempt to provide a full understanding of the nature of these abnormalities within the realm of the medium within

which they are expressed i.e. psychological phenomena (the 'mind') and physiology (the brain)(Frith, 1992). When this has been completed then the conditions may be correct for a mapping of one onto the other, any attempt to do so before merely adds to a confusing of different types of explanation which are inadequate at either level of interest. The focus of this thesis, therefore, is to provide an explanation of the nature of schizophrenic symptomatology at a psychological level, or more accurately in terms of information processing or neuropsychology.

The term neuropsychology, here, is the study of the relation between brain function and behaviour. In effect, it tries to bridge the gap between the behavioural expressions of the illness and any underlying biological abnormalities by addressing the behaviour as an expression of underlying cognitive impairment that in turn may have a biological substrate. It has been remarked that 'The only way to understand psychological phenomena is in terms of psychology' (David, 1993) and this is how we hope to attempt to investigate, through various studies, the nature of schizophrenic symptomatology in cognitive terms. Frith and Done (1988) suggest that there is now a need to develop neuropsychological theories that are able to link the abnormal experiences of schizophrenic patients to malfunctions in specific brain systems.

Much theorising about the underlying cognitive deficits associated with schizophrenic symptomatology follows from neuropsychological investigations of patients with known

brain insults. As schizophrenic symptoms show many common behaviours to those following specific neurological damage, the use of standardised neuropsychological measures has been used in schizophenia research to provide an explanation of characteristic cognitive impairments associated with the disease (see Schizophrenia, the frontal lobes and executive functioning). This approach has been criticised for not addressing the heterogeneous nature of schizophrenia and not concentratring on associations between symptoms and test results (Frith, 1992).

In summary, increasing bodies of evidence from the study of neurological patients, animal studies and psychopharmacological studies in humans, are enabling theorists to produce increasingly more sophisticated modelling of the cognitive deficits underlying the symptoms of schizophrenia, to link the putative biological and behavioural dimensions of the disease.

1.2.1 Early models

Initially, it was Broadbent's (1958) theory of a filter mechanism, for excluding all but relevant information from an individuals perception, that was taken up by researchers concerned with neuropsychological models of schizophrenia. Venables (1964) suggested that the schizophrenic patient suffered an overload of environmental information due to the failure of this mechanism. Frith (1979), in his own version of this 'defective filter theory' proposed much the same, implying that a malfunction existed affecting how the schizophrenic handles external information. However, this level of inquiry was to be rejected on the basis of a lack of experimental evidence (Frith and Done, 1984; 1988).

Cohen (1978) had already stressed that speech production rather than perception lay at the heart of the schizophrenic abnormality. Hemsley (1975) had also proposed that an output filtering problem or response selection constituted the essence of the abnormality. The problem seemed, therefore, to lie in terms of self-generated action difficulties rather than those of perception. Hemsley (1975), therefore, argued that positive symptoms could be explained in terms of a patient's experience of his or her own actions rather than their perception of the external world.

1.2.2. Recent models

Frith (1987) ascribed positive symptoms to a fault in the internal labelling of action i.e. thought insertion, broadcasting and auditory hallucinations could arise due to an inability to label self generated thoughts as 'my own'. The medium for this incapacity is a malfunction in the line of information which travels to an internal monitor which is necessary for the rapid feedback of errors in perception. This system distinguishes between self generated (spontaneous) action and stimulus driven action (Passingham, 1987; Frith and Done, 1988). When information about self generated actions fails to reach the monitor the patient will experience themselves carrying out behaviour without the willed intention to do so. Experimental evidence has supported the proposal that schizophrenic patients have significantly greater difficulty correcting errors in internal monitoring compared to groups of other psychotic patients and normals (Frith and Done, 1989). Frith and Done (1988) proposed a model linking the failure to monitor action and intention with the failure of putative brain structures involved in planning and goal directed behaviour. Goldberg (1985) had suggested that damage at any point from the prefrontal cortex to the motor cortex would lead to an incapacity in self generated

responding. Such a malfunction would account for, at least, some of the positive symptomatology characteristic of schizophrenia. Frith and Done conform to the idea that the hypothesised monitor (sometimes known as a 'comparator') may be functionally related to the hippocampal system. This ties in with the purported role(s) of the hippocampus as the site necessary for recognition memory and familiarity (Gaffan, 1983) and working memory (Olton, 1983). In conclusion, therefore, a failure in internal monitoring has been more specifically attributed to a malfunction of the linkage between the prefrontal cortex and the hippocampus via the parahippocampal cortex and the cingulate cortex (Frith and Done, 1988).

The same authors proposed a wholly different mechanism to account for the expression of characteristic negative symptomatology. After Crow's (1980) suggestion that negative symptoms have a distinctly different aetiology than positive symptomatology it is likely that, in this instance, the incapacity is in generating behaviour rather than a failure to monitor it. This inability (to generate spontaneous action) is thought to be due to a malfunction along the pathway(s) joining the prefrontal lobes to the striatum.

1.2.3 Schizophrenia as a disorder of self-awareness: Frith (1992) model

Frith (1992), in an attempt to provide a cognitive neuropsychological explanantion of the signs and symptoms of schizophrenia, suggested that the underlying cognitive abnormality was one of a disorder of self-awareness. Expanding on his previous work singularly and in collaboration, expounded above, Frith suggests three principal abnormalities underlying all the major signs and symptoms of the illness. Firstly, disorders of willed action or the inability to generate spontaneous (willed) action can lead to

poverty of action, perseveration and inappropriate action. In essence, that behaviour is elicited by external stimuli only. Secondly, certain auditory hallucinations and delusions including thought insertion and alien control can be attributed to a disorder of self monitoring (see above). Finally, core symptoms such as delusions of reference, paranoid delusions, third person auditory hallucinations and certain types of incoherence i.e. characterised by speech patterns lacking the use of previously qualified referents, may be caused by a disorder in monitoring the intentions of others. Frith goes on to explain that these three pathways to symptom expression may be due to an abnormality in a single fundamental cognitive process necessary for consciousness. This process is termed metarepresentation. In other words, the schizophrenic patient has difficulty reflecting on how s/he represents the world and their own thoughts. To have self-awareness one must be able not only to experience the content of what is happening mentally or physically, but one must have knowledge of how that experience is being represented itself i.e. is the experience my own, as in 'I am watching a football match'- 'I am watching' is the self-conscious (secondary) representation of the (primary) representation 'a football match'. For instance, if something is being attended to one must have representational knowledge concerning that attention otherwise the experience is not part of consciousness. If this mechanism breaks down then one only experiences content not the appropriate knowledge of how that content is represented in the world. Frith believes such a failure of metarepresentation can lead to a lack of awareness of goal directed behaviour and awareness of personal and interpersonal intentions. These abnormalities derived from a failure in the mechanism of self-awareness account for the three pathways of cognitive impairment responsible for the signs and symptoms of schizophrenia cited above. As this is a relatively recent model, of the cognitive abnormality underlying schizophrenic signs and symptoms, it is too early to accurrately map the theory onto specific brain systems.

However, as the cognitive mechanism at fault is one of self awareness then a failure in metarepresentation would imply dysfunction in a distributed brain system involving structures and systems necessary for goal directed behaviour, action, willed intentions and social cognition i.e. facial recognition etc. Although specific experimental evidence of metarepresentation is, only starting to accumulate, at time of writing, greater understanding of the neural correlate(s) may be gleaned from animal studies and human investigations using scanning technology such as PET (Frith, 1992).

1.2.4 Schizophrenia as a disorder of the integration of memory on current perception: Gray et al (1991) model

One of the most comprehensive models to appear in recent years has been formulated by Jeffrey Gray and his colleagues at the Institute of Psychiatry in London. Particularly concerned with integrating the neural and cognitive dimensions of acute or the positive symptomatology of schizophrenia, Gray et al (1991) have combined two major neuropsychological models that were already established in the literature; Frith's (1987) and Hemsley's (1987) models.

Frith (1987) and expanded by Frith and Done (1988) has already been discussed (see above). Hemsley's (1987) theory holds an alternative view with it's history grounded in Broadbent's (1977) theory of the 'pigeon holing' of information during processing. The problem for the schizophrenic patient, Hemsley argued, resulted from a weakening of the influence of stored memories of regularities of previous input on current perception. In other words, there is a weakening of the capacity to select for cognitive processing only those stimuli, that, given past experience of similar contexts, are relevant. Cognitive

abnormalities in schizophrenia are thus seen as associated with a weakening of inhibitory processes crucial to conscious attention. Hallucinations, therefore, are intrusions into conscious experience of material from an individual's long term memory which are then attributed to an external source.

Gray et al (1991) emphasised that, at the core of their model, there exists "...a failure in acute schizophrenia to integrate stored memories of past regularities of perceptual input with ongoing motor programmes in the control of current perception" (p.1).

1.2.5 Gray et al. model in detail

Evidence in support of the model was obtained from three major sources; studies into brain neuropathology and experimental evidence involving animals and humans. In considering brain dysfunction in schizophrenia, two main avenues of evidence may provide a more unified picture of the putative 'schizophrenic brain'. The first of these is the widely documented number of dopamine receptors observed in both post mortem (Owens et al, 1978) and in vivo (Wong et al, 1986) brains of schizophrenic patients. Elevated numbers of receptors support a dopamine hyperactivity hypothesis connected, at least, with positive symptomatology. Secondly, post-mortem studies of the brains of schizophrenic patients have revealed severe neuronal loss in several regions of the temporal lobe (parahippocampal gyrus, hippocampal formation, cingulate cortex and the amygdala) (Falkai and Bogerts, 1986). A link between these two phenomena could paint a more united picture of brain dysfunction in the schizophrenic patient. Springer and Isaacson (1982) demonstrated that damage to the hippocampal formation alters dopamine

transmission in the nucleus accumbens and is indicative of a functional increase in transmission.

The second line of evidence for the model can be derived from animal studies. In particular, the behavioural phenomena of Latent Inhibition (Lubow et al, 1982), the Kamin blocking effect (Lubow, 1968) and the Partial Reinforcement Extinction Effect (PREE; Gray et al, 1975) have been proposed as animal models, that when disrupted, act as the basis for the cognitive dysfunction underlying schizophrenia. Gray et al (1991) argued that such effects provide 'face validity' as comparative processes. Each, the argument goes, can be considered as examples of the influence of stored memories of regularities of previous input on current perception (Hemsley, 1987); PREE specifically in terms of motor programming. Each of these phenomena have been shown to be abolished by amphetamine which is a dopamine releasing psychomimetic drug (Crider et al, 1982). In addition, the effects of Latent Inhibition (Solomon et al, 1981) and the Kamin blocking effect (Crider et al, 1982) can be reversed by neuroleptic administration. The amphetamine treated animals in these experiments behave as though their current perception of pre-exposed stimuli (of non-reward) are less influenced than normal by experience of previous regularities of input. The functional dopamine overactivity tends to result in a certain degree of 'overattention' in their perception of current stimuli. However, in the present formulation Gray et al., stipulated that the disruption of the subiculo-accumbens projection should yield the same consequences as the above experimental amphetamine administration. Large hippocampal lesions have been used to destroy this projection and subsequent experiments have shown that Latent Inhibition, the Kamin blocking effect and the PREE are all disrupted by damage to the hippocampal formation (Kaye and Pearce, (1987).

As far as human subjects are concerned, acute schizophrenic patients fail to display Latent Inhibition and the Kamin blocking effect (Baruch et al, 1988b; Jones, 1989,1991) although these phenomena have been observed in groups of chronic schizophrenic patients. Gray et al suggested that the presence of Latent Inhibition in chronic schizophrenia is possibly due to neuroleptic effects. However, these results highlighted the fact that Latent Inhibition is not just a nonspecific consequence of the generally poor cognitive levels characteristic of schizophrenia.

The Gray et al (1991) model provided a single appreciation of the neuropsychology of the positive signs of schizophrenia, grounded in the previously formulated theoretical paradigm of the neuropsychology of anxiety (Gray, 1982). Within this paradigm the septohippocampal system, together with a number of other limbic structures related closely to the septohippocampal system, are associated with a monitoring or 'comparator' function (see Frith and Done, 1988).

The overall model proposed that the establishment of a sequence of steps in a motor programme and its orderly running are guided by the projection from the amygdala to the nucleus accumbens. The septohippocampal system checks whether the actual outcome of a motor step matches the expected outcome- this information is transmitted to the nucleus accumbens by the projection from the subiculum. The activities of these interacting structures are purported to be coordinated by the prefrontal cortex.

The maintenance of the activity in the structures that make up a motor step result from excitatory activity in the striatum- these patterns are sometimes disrupted by the firing of

dopamine inputs to the striatum. Duration corresponds to the cooperation of the caudate system (having many specific connections with the sensory and motor cortices) and the nucleus accumbens system. Timing is coordinated between the comparator and the basal ganglia. The caudate system and the nucleus accumbens are also believed to play an important role in organising behavioural response to novelty and controlling interactions between such responses and motor programming.

The model is, therefore, when applied to the cognitive abnormalites associated with acute schizophrenia, a disorder of motor programming and monitoring. The Hemsley (1987) component concerned with the effect of previous experience on programming finds neuroanatomical reality in the form of the subiculo-accumbens projection- such a projection, in this case, thought to be impaired in schizophrenia. Frith's (1987) proposal concerning the monitoring of willed intentions finds its equivalent as the projection from the subiculum to the nucleus accumbens- again inferring that schizophrenic symptomatology occurs as the result of the disruption of the subiculo-accumbens projection. In addition, as the septohippocampal monitoring system, via the projection from the prefrontal cortex to the entorhinal and cingulate cortices, is provided with the motor programming information, disruption anywhere along these routes could also be disrupted in schizophrenia.

Gray et al (1991) admitted that further knowledge of brain pathology is needed before any speculations to which of the proposed circuitry disruptions is primary. Nor, presently, does the model speculate as to any indication of aetiology. The model is restricted to demonstrate those malfunctions that are related to the cognitive abnormalities associated with the positive symptoms of acute schizophrenia. Finally, the authors admonish, it

would be somewhat astonishing if the myriad of abnormalities expressed by the schizophrenic were always echoes of the same neuropsychological dysfunction.

As far as an explanation of the cognitive abnormalities associated with negative symptoms are concerned, Gray et al (1991) posited that the actual nature of the concept is problematic. For instance, are those sets of symptoms traditionally bracketed as positive and negative representative of distinct disorders, differing severities of the same disorder, due to individual differences to the same or different stages of the same disorder or, indeed due to a combination of any of these? In fact, negative symptoms, in the context of the model in question, are seen rather as representing a severity threshold on a continuum of schizophrenic symptoms (Pogue-Geile and Harrow, 1988). Hemsley (1972) proposed that, on the whole, negative symptoms replace positive symptoms, over time, in prominence and that the concomitant cognitive deficits due to 'information overload' seem to go someway to complete this picture. Negative symptoms such as social withdrawal, poverty of speech and autism are seen, in this light, as adaptive strategies, on the part of the individual, to minimize the effects on themselves of their cognitive impairment. The schizophrenic is seen as perceiving the pursuit of meaning as increasingly ineffective or counterproductive. In line with Anscombe (1987), when displaying negative symptoms the schizophrenic forms their own impressions less and less and becomes increasingly and eventually wholly influenced by their environment.

1.2.6 Criticism of the Gray et al. model

The Gray et al (1991) model is one of the most comprehensive efforts to attempt a detailed and testable account of the neuropsychology of schizophrenia. As this enterprise

was somewhat ambitious, 36 leading researchers were invited to provide their own criticisms of the model.

Claridge and Beech (1991) criticised the restrictive use of animal studies as models for a distinctly human pathology. However, Frith (1991) applauded the use of animal studies as a valuable tool in what he describes as a particularly experimental field. Dawson and Hazlett (1991) stated that not all behavioural phenomena, relying on memories for past regularities, adhere to the model. Early et al (1991) provided evidence that hippocampectomy does not produce signs of psychosis. Additional criticisms encapsulated the failure of the model to include laterality studies (Elkins and Cromwell, 1991) and questioned the centrality of the dopamine hypothesis as neuropathological evidence (Hoffman, 1991).

Frith (1992) provided a major criticism of the methodology of the Gray et al. model. He argued that the authors have attempted to link animal behaviour to the symptoms of schizophrenia in terms of impairment in task performance i.e. Latent Inhibition, rather than as underlying cognitive processes. However, within this task performance paradigm, using Proactive Interference (PI) as a model of Latent Inhibition with human subjects, O'Carroll et al (1993) found no significant differences, using the Auditory Verbal Learning Test (Rey, 1964) as a PI measure, between groups of acute unmedicated schizophrenic patients, major depressives and controls. The group of schizophrenic patients would have been expected to show reduced PI compared to the other groups based on the animal data from LI studies-they demonstrated, however, in this instance, similar levels of PI to the comparison groups. However, the PI paradigm in the O'Carroll et al. (1993) study did not involve associate learning, whereas Latent Inhibition studies

do. O'Carroll (1995) utilised a paired learning paradigm and found that acutely ill schizophrenic patients were just as affected by previous experience as chronic patients. Gray et al.'s model, therefore, has not been supported experimentally which may necessitate an elaboration of their findings beyond such a task performance paradigm as schizophrenic symptomatology in humans would appear to require a more sophisticated cognitive explanation than can be derived from a behavioural model based largely on animal studies.

A major area of criticism, however, dealt with problem of focusing on the positive symptom dimension of schizophrenia (Ingraham; Manschreck and Maher, 1991). Also, positive and negative symptoms have been shown to coexist over long periods of time (Andreasen, 1985). On the other hand, Crider (1991) applauded the model as giving justification for rethinking the contemporary neglect of the motor manifestations of schizophrenia. Crusio (1991) agreed that damage to the hippocampal system is a good candidate for the primary lesion that leads ultimately to the symptoms characteristic of schizophrenia.

Gray et al. (1991) model provided a contemporary attempt to account for the positive symptoms of schizophrenia within a behavioural paradigm. Pathways of associated neural dysfunction that may be implicated as underlying the fundamental cognitive impairment are provided. However, this is an ambitious undertaking and, although open to the criticisms expressed above, shows the type of rigour and complexity of knowledge to provide an integrated explanation of schizophrenic symptomatology. A major contribution of the main tenet of the model, that of an impairment in the access of previous regularities of input on current functioning, has highlighted the potentially

fundamental role memory deficits appear to play in the expression of schizophrenic symptomatology that has also been supported by evidence from other methodolgical persuasions from the literature on the neuropsychology of schizophrenia (see Memory and Schizophrenia).

1.3 Schizophrenia the frontal lobes and executive functioning

As stated above, a popular method of investigating the relationship between the behavioural abnormalities and putative underlying brain abnormalities associated with schizophrenia has been to use neuropsychological information derived from patients with localised brain damage. Much of the focus for such research has centred on analogy with patients with known damage to the frontal lobes. There appear to be many core behavioural characteristics that are common to both frontal and schizophrenic conditions. Patients with frontal damage display behaviours such as stereotypy or perseveration, poverty of activity and inappropriate responding to stimuli (Luria, 1973; Frith, 1992) which are commonly expressed by patients diagnosed with schizophrenia. Specific neuropsychological tests have been applied to patients with frontal insults allowing subsequent identification of tests that can be associated with specific areas of damage. Such tests have then been administered to various groups of schizophrenic patients in an attempt to clarify the nature and degree of the neuropsychological impairment associated with their behavioural dysfunction. According to Gur et al (1990) there are two main types of clinical neuropsychological test battery. The first is 'fixed' and includes a comprehensive set of tests eg the Halstead-Reitan battery (Reitan and Wolfson, 1985). A 'flexible' battery, on the other hand, includes a core set of tests plus a sample of selected tests of functional domains to investigate specific hypotheses. Either of these schemes

allows a comparison of schizophrenic patients with other patient groups and/ or normals. One aim of such testing has been to infer the region of brain dysfunction responsible from the pattern of the functioning deficit.

The particular core behavioural impairments associated with frontal lobe patients have been termed the 'Dysexecutive Syndrome' (Baddeley, 1986) and include disturbed attention and increased distractibility (Baddeley and Wilson, 1988) as well as the problems in activity stated above. Shallice (1988) suggested that the 'frontal' patient's behaviour could be due to an impairment in the control of action where activities are chosen by a process of mutual inhibition, the most highly 'activated' winning its way towards being carried out. This process works if environmental cues are present for the selection of appropriate behaviour. Without such cues there is no activity or perseveration occurs. However, often responses to environmentally driven behaviours need to be modified or even overridden by a 'supervisory attentional system' (SAS) which can activate actions not dependent on environmental stimuli. This can prevent perseveration, inhibit inappropriate responses and produce new action plans rather than routine ones despite the environment. Frontal-type behaviours are, therefore, resultant of an impairment in this mechanism.

1.3.1 Neuropsychological testing and frontal lobe/executive functioning

Regional brain function, associated with the frontal lobes, has been investigated using measures such as the Wisconsin Card Sort Test (Heaton, 1981) and the Halstead Categories Test (Reitan and Wolfson, 1985) designed to measure higher levels of abstraction and mental flexibility. Deficits related to the frontal system have also been associated with poor performance on Trails A and B tests (a measurement of mental flexibility and motor function) (Reitan and Wolfson, 1985) and measures of verbal and figural fluency (Miller, 1984). These tests have been found to be sensitive to specific frontal lobe lesions in neurological patients (Ramier and Hecean, 1970). The disruption is usually associated with particularly anterior lesions resulting in disorganisation of goal directed behaviour related to attentional processing and conceptual flexibility (Goldberg et al, 1987).

The Wisconsin Card Sort Test has been described as 'the best available test of dorsolateral frontal cortex function' (Kolb and Wishaw, 1990 p.487). Requiring a selection of cards varying in three perceptual dimensions (shape, form or colour), the subject must continuously pick a card according to one dimension on the basis of trial and error and feedback from the tester only. When a criterion is reached the rules are changed. Those subjects with frontal lobe dysfunction tend to attain fewer categories of set- usually as a result of perseverative responding due to performance related to the previously correct dimension (Milner, 1964)- this effect is particularly prominent with lesions to the dorsolateral prefrontal cortex (Weinberger et al, 1986). However, damage to regions outside the frontal cortex can also produce similar deficits (Drewe, 1974).

The deficits revealed by use of the WCST can be interpreted in one of several ways. There may be an inability for abstract thought or for concept formation, for selective attention or for shifting cognitive set. Frith (1987) predicted that schizophrenic patients would perform poorly, on the WCST, due to an inability to plan or monitor responses appropriately in the face of changing circumstances. Particularly poor performance has been observed in schizophrenic patients displaying predominantly negative symptomatology, indicated by high numbers of perseverative errors (Weinberger et al, 1988). The same authors have shown a correlation between the degree of 'hypofrontality' in their patient sample, as measured by the WCST, and cerebrospinal fluid levels of the dopamine metabolite, homovanillic acid (HVA). This was interpreted as reflecting a decrease in mesocortical dopamine activity. However, Braff et al (1991), in a study of medicated chronically ill schizophrenic patients, found that their sample displayed relatively few perseverative errors on the WCST. Although this could reasonably reflect medication effects, a subgroup of particularly disturbed patients did demonstrate a significant impairment in performance. Therefore, 'hypofrontality', as assessed by WCST results, appeared to be associated with the more deteriorated or 'Kraepelian' patients in this sample.

Some authors have argued that while interpreting the significance of WCST results there may be a disagreement concerning the significance and specificity of such performance when compared to other deficits expressed in schizophrenia. Tests such as the WCST appear to tap multiple processing abilities and thus performance may be due to dysfunction in structures outside the frontal lobes. For instance, patients suffering basal ganglia disorders eg. Parkinson's Disease and Progressive Supranuclear Palsy have been seen to produce poor WCST results and, therefore, may also be involved in the

expression of 'hypofrontality' (Weinberger, 1986, 1987). In fact, the use of the WCST has been seen as having reached its peak by some authors as to what new information it can relay about schizophrenic functioning (Corcoran and Frith, 1993). In the event, the use of such a tool has been advocated within a broader appreciation of schizophrenic neuropsychology and its putative underlying neuropathology (Kolb and Wishaw, 1983).

Gur et al (1990) using the WCST and the Californian Verbal Learning Test (a measure of memory and learning, (Delis et al. (1983) found that their sample of patients were impaired on both measures. The results showed, however, that the impairment in memory and learning was significantly worse than the impairment seen in the WCST performance. The authors believed their study supported a selective and disproportionate temporal lobe dysfunction in their sample of schizophrenic patients. Support for a differential frontal lobe dysfunction in schizophrenia was not found. Memory and learning, after profile analysis, were significantly worse in comparison to all other functioning than functioning as measured by the WCST results. Troubled by this specificity of the results and the probability that a constellation of other deficits may implicate other specific brain regions, Gur et al (1990) developed an algorithm of 'behavioural imaging' in an attempt to provide a standard regional interpretation of their neuropsychological data. Using PET scans, along with the data from neuropsychological measures, the algorithm yielded values for specific regions reflecting a prediction that a region is dysfunctional given the pattern of neuropsychological scoring. As the prediction indicated, the authors found that the frontal and temporal lobes were implicated (as dysfunctional) in the impaired performance on the WCST and the CVLT. However, the authors also warned that such 'behavioural imaging' awaits further verification. This approach, they suggested, is more appropriate when considering a functional model of schizophrenia, providing functional imaging data

when individuals are engaged in neurobehavioural tests that are known in normals to activate specific brain regions. A disproportionate and selective impairment in memory and learning tests was also reported by Saykin et al (1991) but not on tests purportedly sensitive to 'frontal lobe' functioning. In this case the sample of patients were unmedicated. The authors interpreted such a pattern of functioning as involving dysfunction of the temporal-hippocampal system (against a background of diffuse impairment). Gruzelier et al (1988) had also reported that the selectivity of neuropsychological dysfunction their group implicated temporal-hippocampal dysfunction.

An intensive case-study approach, using a wide range of neuropsychological tests, including many putatively sensitive to 'frontal' functioning has been used to examine the pattern of dysfunction in schizophrenia (Shallice et al,1991). The authors stated that, despite overall ability, all patients performed badly on tests 'sensitive' to frontal functioning, particularly verbal fluency. They concluded that, although the 'frontal' test performances were significantly impaired relative to the background level of cognitive functioning, the performance between individuals was markedly heterogeneous not only in their degree of impairment but in their patterns of performance. This indicates that the interpretation of the results of such testing could be misleading if group means are considered alone. The authors admonished subsequent researchers to take the heterogeneity of functioning seriously, when interpreting neuropsychological test results, as this dimension of the disease may possibly be its most characteristic. Such conclusions also provide support for analyses of the patterns of neuropsychological functioning with symptom profiles.

A broader appreciation of a specifically 'frontal' hypothesis of schizophrenia has been elicited through activation studies. Weinberger et al (1986), using regional cerebral blood flow measures, found an increase in rCBF during the WCST in normals but not with a group of chronic schizophrenic patients. Therefore, the inability of the patient sample to do the test was attributed to an impairment in frontal lobe activation. The authors argued that, in the light of previous animal studies, the results were consistent with a lesion involving the dopamine innervation of the dorsolateral prefrontal cortex. Following on from this, the authors argued, that the primary abnormality could be due to subcortical pathology. However, Goldberg et al (1989) found that the pattern of functioning observed in affected twins of monozygotic pairs results implied frontal-temporal dysfunction with relative sparing of posterior and subcortical functioning. Despite this, Pantelis et al (1992) in a review of the evidence for a frontal-subcortical pathology argued that the neuropathological and neuropsychological data, to date, revealed an intimate relationship between these brain regions. In line with Weinberger et al (1986) and Pantelis et al (1992), Brown and White (1992) expressed support, of subcortical involvement, having demonstrated that the degree of Tardive Dyskinesia displayed by their patients was significantly associated with the degree of impairment on tests sensitive to 'frontal' functioning (including the WCST). Subcortical pathology was, therefore, implicated in determining the pathophysiological mechanism through which 'frontal' functioning is impaired. Therefore, dysfunction should be seen in terms of system abnormalities whose components may include regions previously connected with particular patterns of neuropsychological test performance, including the WCST, (Robbins,1990). However, to date, there is much controversy concerning which systems are of primary concern for the researcher.

Because of the aforementioned problems with goal-directed activity in both 'frontal' and schizophrenic patients, another popular neuropsychological measure used with these patients is the Tower of Hanoi or London Test (Shallice, 1982). This test appears to assess organisational and strategic planning ability. The subject is required to move discs or balls from an initial to a goal position. Subjects are encouraged to think their solutions through before activating their sequence of goal directed moves. Shallice (1982) found that patients with anterior cortical damage made more errors than those with posterior cortical damage or controls. Owen et al (1991), using a computerised version of Shallice's test, found that subjects who had undergone surgery on their frontal lobes for epilepsy or tumours made more errors and were slower than controls to instigate their solutions subsequent to their first move. Nelson et al (1991) compared test results with Liddle's (1987) syndrome typing of schizophrenia. They found an association between Tower of London scores and the 'psychomotor poverty' syndrome, implicating more of a poverty of action impairment than disorganisational component with regard to the test demands.

Saint Cyr et al (1988), in a comparison with Parkinson's disease and Huntington's disease patients (both resulting from basal ganglia dysfunction), found that schizophrenic patients performed worse than the Parkinson's disease patients and a sub group of the Huntington's patients on a three disc (problem) version of the 'Tower' test. However, the schizophrenic patients performed better than the other two groups on a four disc problem. The performance of the schizophrenic patients was characterised, the authors suggested by 'frontal' rather than basal ganglia dysfunction. The four disc problem was seen, rather, as a test of procedural learning than planning ability, the former allegedly associated with basal ganglia function.

It seems increasingly relevant to consider the pattern of schizophrenic functioning, observed on a wide range of neuropsychological tests, as reflecting different combinations of cortical damage perhaps with interactions at a subcortical level (Robbins, 1990). It remains that to interpret neuropsychological results as region specific is fraught with problems not only from a neuropathological view but also from an over optimism surrounding the specificity of the measures presently in use i.e. most 'frontal' tests demand multiple processing. The analogy used of the focal neurological patient as model for the putative pathological problems associated with schizophrenia appeares to necessitate the incorporation of more intensive approaches to appreciate the difference between individuals on their test performance but that also test performance, in turn, ought to be assessed in light of symptom profiles or with more homogeneous groups. Schizophrenic neuropsychology appears more than an extension of a specific neurological insult i.e. a 'frontal' impairment, multiple functions are apparently impaired. Future studies must integrate what we have learnt about 'frontal' or executive functioning in context of other areas of disproportionate dysfunction, to produce an integrated scenario of characteristic neuropsychological impairments responsible for the expression of particular symptoms.

1.4. Long term neuropsychological deficits and Symptoms

In a recent study, on a sample of 58 chronic schizophrenic patients, after a follow up period of between 2 and 12 years, 'substantial' functional cognitive impairments were observed (Breier et al, 1991). Performance on neuropsychological tests allegedly sensitive to frontal cortical functioning (Wisconsin Card Sort Test, Trails A&B, Word Fluency) were significantly correlated with the outcome levels of negative symptom ratings and

social functioning measures rather than with positive symptom levels. The authors proposed that the lack of a relation between positive symptoms and putative measures of 'frontal' cortical functioning suggests that the symptom components of the schizophrenic condition may have distinct anatomic origins. From their results the authors attempted to charter the course of a 'typical' chronic illness. This, they argued, is characterised by deterioration, stabilization and, finally, (slight) improvement phases. This 'model' was linked to dopamine alteration in activity ie high dopamine activity was associated with initial deterioration. Slowing of deterioration and subsequent improvement may be related to a decrease in activity associated with the normal aging process (Wong et al, 1984). The study can be severely criticised by the lack of 'non frontal' control tasks in the methodology.

Nelson et al (1990) compared symptomatology with neuropsychological profiles, in chronic schizophrenic patients. They investigated the relation between motor and cognitive speed and symptomatology, finding that it was the severity of negative but not positive symptoms that was related to the severity of the patients bradyphrenia (cognitive slowing). Cognitive speed appeared more affected than motor speed. In line with Pantelis et al (1989b; 1992) and Crow (1980), they argued that such observations are consistent with a subcortical pathology in patients with type 2 schizophrenia. [Rogers (1986) had suggested that bradyphrenia was the fundamental phenomenological feature of the subcortical dementias.] Overall, cognitive functioning, unsurprisingly, was significantly depressed compared to normals. However, evidence of significant levels of below average premorbid intelligence (NART scores) was evident in their sample. These findings have not been replicated by other researchers with similar samples (Bilder et al, 1988; Frith et al, 1991), although compromised NART scores have been observed with

long term hospitalised schizophrenic patients (Crawford et al., 1992), implying poor pre morbid functioning to be associated with the more resistant and deteriorated form of illness. These results may, alternatively, question the use of the NART as a pre morbid measure unaffected by the disease process.

In the Frith et al (1991) study a comprehensive battery of neuropsychological tests was administered to a sample of 283 schizophrenic patients. Despite no overall impairment in premorbid functioning, a relationship was found between low premorbid IQ scores and subsequent symptoms in their large sample. These patients exhibited more severe negative features of the illness. Again, low pre morbid functioning tended to be associated with the more severely deteriorated patients. The authors found that, in terms of cognition, schizophrenic features fell into one of three distinct categories. Firstly, hallucinations and delusions had very little effect on the cognitive processes examined. The presence of poverty of speech, flattened affect and motor retardation, however, were strongly associated with cognitive dysfunction such as deterioration in IQ scoring, verbal fluency and forced choice recognition. Incoherence of speech and incongruity of affect were also strongly associated with cognitive dysfunction this time independent of negative features. These were associated with the failure to inhibit inappropriate responses (as measured by a continuous performance test) and also with the production of unconventional responses in a verbal fluency task.

Again Frith and his colleagues noticed a difference between the impairments associated with positive and negative symptoms respectively. The authors suggest that this could reflect the true nature of the two types of features. Negative symptoms are possibly,

therefore, primarily associated with a failure to respond, positive signs being associated rather with the production of a wrong/inappropriate response.

The 'traditional' positive-negative dichotomy, involved in many of the studies presented above, has recently been clarified in terms of 'type 1' and 'type 2' schizophrenias in order to describe the heterogeneity of the condition (Crow, 1980; 1985). However, even the clusters of symptoms subtyped by Crow have been seen as mutually inexclusive i.e. can exist simultaneously in the same individual and, thus, present difficulties in clarifying the underlying associated pathological processes. Therefore, this may lead to confusion associating pathology directly with symptom type (Liddle and Barnes, 1990).

In order to provide a clearer empirical delineation Liddle (1987a, b) factor analysed symptom ratings into clusters or sub-syndromes of illness and correlated them with patients' neuropsychological test performance (Frith et al, 1991 followed similar methodology). Liddle's methodology revealed three distinct sub-syndromes. The syndromes which emerged were; firstly, 'psychomotor poverty' associated with deficits in abstract thinking and long term memory, 'disorganisation' associated with poor concentration and difficulty in learning new material and, finally, 'reality distortion' associated only with limited cognitive dysfunction, found only in poor performance in figural/ground perception measures. The first two of Liddle's syndrome types have been associated with putative 'frontal lobe' deficits while 'reality distortion', the author argued, is related to temporal lobe dysfunction (Liddle, 1987). Such results have been supported by further neuropsychological studies (Liddle and Morris, 1991). In this study slowing of mental activity was particularly associated with 'psychomotor poverty' while 'disorganisation' was associated with tests where the subject failed to inhibit an

established but inappropriate response. 'Reality distortion' was not significantly correlated with such traditional putative 'frontal lobe' measures. This type of syndrome generation has been particularly useful in composing a tripartheid syndrome typing of chronic schizophrenia (Liddle and Barnes, 1990). A final area of support, and direction for further study, has come from PET studies which have confirmed the three syndrome associations with particular brain regions. Liddle et al. (1992) again found, via factor analysis, symptom ratings from a sample of stable chronic schizophrenic patients could be successfully separated into the three syndromes cited above. PET scanning was used to record brain functioning due to the degree of cerebral brain blood flow. The study confirmed earlier predictions in so far as 'psychomotor poverty' and 'disorganisation' were associated with altered perfusion at different loci in the prefrontal cortex. 'Reality distortion' was associated with altered perfusion in the medial temporal lobe. However, the patterns of perfusion observed suggested that any abnormalities of brain function underlying each syndrome are of a more complex nature and involve abnormalities in distributed neural networks and are not confined to single loci.

Close study of these groups of chronic schizophrenic patients shows that there appears to be a clear association between negative symptomatology and impaired cognitive performance. Any characteristic impairment profile is, as yet unforthcoming. However, recent research, seems to be pointing to an appreciation of long term or chronic schizophrenia as a disseminated entity, expressed most probably as groups of related clusters of symptoms, each possessing a particular neuropsychological profile and thus indicative of distinct pathophysiologies.

1.5 Memory and Schizophrenia

Memory impairments have been implicated in the neuropsychological mediation of symptoms in the models of Gray et al. (1991) and Frith (1992), in terms of accessing appropriate previously learnt knowledge for present functioning and knowledge of second order representations necessary for self-awareness, respectively. Evidence from neuropathological sources has shown changes in the medial limbic structures of the temporal lobe including the hippocampus, in groups of schizophrenic patients, suggestive of an underlying biological substrate associated with the putative memory deficits (Bogerts et al, 1985). However, up until relatively recently, authors have dismissed memory impairments as of little importance in the understanding of the psychology of schizophrenia (e.g. Cutting, 1990). Despite this, recent research has accummulated supporting a central role for memory problems as an underlying neuropsychological deficit responsible for the expression of certain schizophrenic symptoms.

McKenna et al (1990) tested a group of 60 schizophrenic patients, of all grades of severity of illness, on a wide range of memory tasks. A substantial deficit in long term episodic memory functioning was recorded disproportionate to the degree of their general cognitive impairment. The authors believed the underlying dysfunction was similar to that of the Classic Amnesic Syndrome (CAS; Baddeley, 1982) (where an intact short term memory but wide ranging deficits in long term memory are observed). This pattern resembled the dysfunction seen in Korsakoff's syndrome rather than in Alzheimer-type-dementia (sufferers of ATD display deficits in both short and long term memory). The deficits were not attributable to the effects of medication but appeared as a function of the severity and chronicity of the illness. Tamlyn et al. (1992) and Duffy and O'Carroll

(1994) have also observed disproportionately impaired long term episodic memory functioning with their patient samples. In an analysis of this episodic memory impairment, Clare et al. (1993) found schizophrenic patients' word and face recognition memories and prose recall to be equally compromised compared to matched controls. However, Calev et al. (1984) found recall deficits to be more severe than recognition deficits when using tests matched for degree of difficulty. Tamlyn et al. (1992) also found that semantic memory was disproportionally impaired compared to general intellectual impairments. Interestingly, Duffy and O'Carroll (1994) found, in a comparison with a group of Korsakoff's patients, a disproportionate semantic memory impairment in their schizophrenic patient and better episodic memory functioning. With respect to symptom expression, semantic memory dysfunction has been implicated in the generation of delusions through an impairment in the continuous gathering and 'reality checking' of knowledge so that false memories are stored which become the false knowledge that are delusions (McKenna, 1991). In addition, in the Frith (1992) model, metarepresentation has been suggested as dependent on knowing the source of one's memory of activity, the impairment of which would putatively compromise one's ability to form second order representations. The memory impairment observed with various groups of schizophrenic patients, from the literature, appears to implicate both episodic and semantic memory impairments as underlying such symptoms as delusions. These observations may be supported by the suggestion that although episodic and semantic are distinct memory systems, they appear to act in a highly integrated way (Parkin, 1987).

The specificity of the memory function to schizophrenia was investigated by Sengel and Lovallo (1983), who tested groups of paranoid and non-paranoid schizophrenic patients, depressed patients and normal controls on their memory for a categorised word list. On

immediate recall the three psychiatric groups benefitted equally when given category cues. The schizophrenic patients alone showed a significant recall deficit in the delayed recall condition regardless of cues. They also lost a number of categories in the non-cued condition suggesting a more fundamental memory problem compared to the other groups. In a study by Harvey et al (1986) both schizophrenic and bipolar patients displayed impaired recall relative to controls. The schizophrenic patients' performance was attributed to encoding difficulties, whereas the deficits incurred by the bipolars was attributed, primarily, to thought disorder.

Although schizophrenic patients may differ from other psychiatric groups in the nature of their memory impairment, it also appears that the memory dysfunction may be selectively dispropotionate to the other widely documented neuropsychological deficits observed with groups of schizophrenic patients. Saykin et al (1991) reported that a group of 36 unmedicated schizophrenic patients showed a selective and disproportionate deficit on memory and learning tasks despite their general cognitive impairment, compared to controls. Such selectivity was not forthcoming on tests allegedly sensitive to frontal lobe functioning. The finding was of additional interest as the results were not contaminated with issues surrounding medication effects or long term hospitalisation. This selectivity had not been documented before and provided support for a hypothesis of temporal-hippocampal dysfunction in the pathophysiology of schizophrenia. Such a conclusion had already been implicated by Gruzelier et al (1988) who concluded that temporal-hippocampal dysfunction most likely explained their schizophrenic patients' poor scores on verbal and spatial memory measures. Saykin et al. (1994) replicated the results of the 1991 study with 37 patients never exposed to neuroleptics in their first episode. However, Blanchard and Neale (1994) found no disproportionate neuropsychological

deficit with sample of 28 patients whose mediaction had been withdrawn for research. Deficits were seen on a range of test performances compared to matched controls.

However, memory impairments do not stand alone as commonly observed neuropsychological deficits associated with schizophrenia. The emerging pattern of impairments would imply multiple impairments of integrated functions and, thus, diffuse pathophysiology. For instance, Schwartz et al (1991) found that a group of chronic schizophrenic patients displayed a significant memory deficit on a recency discrimination task. This was seen as reflecting poor memory for temporal order. This sample was also given the Wisconsin Card Sort Test. Their performances, on the recency discrimination task, were inversely related to the number of perseverative error scores accrued on the WCST. These results, therefore, once more emphasised the important role of putative prefrontal/executive dysfunction aswell as memory dysfucntion in any appreciation of overall neuropsychological dysfunction in schizophrenia.

Since the reemergence of memory dysfunction as a focus for schizophrenia research, workers have attempted to focus on what specific areas of functioning could explain the deficits. Goldberg et al (1989) found that, in a group of 31 schizophrenic inpatients, retrieval of verbal material from the Selective Reminding Task (Bushke and Fuld, 1974) was significantly worse than recognition. However, the schizophrenic patients did show an apparent ability to encode the material by displaying a learning curve during performance. Goldberg et al (1989) postulated that the recall (retrieval) deficit suggested dysfunction of the prefrontal cortex. The mechanism underlying these results was interpreted as differing from that associated with Alzheimer-type-dementia *and* Korsakoff's syndrome both of which are characterised by deficits in verbal recognition

aswell as recall. This is an important observation as recognition memory and recall memory may well be mediated by different neural systems.

Although the pathophysiology of the condition appears to involve dysfuction in several neural systems, Calev et al (1991) showed that, by displaying equal deficits on tests of verbal and visuospatial recall compared to controls, there is little support for a specific verbal memory deficit in schizophrenia-which might be implied due to the nature of positive symptoms. This result, albeit with a small sample, questioned the role of hemispheric differences, which had been widely implicated in schizophrenic performance (e.g. Saykin et al., 1991), in affecting such memory tasks. The basic verbal and visuospatial recall deficits, documented by Calev et al appear suggestive of bilateral hippocampal involvement, particularly in the severely disturbed. Mildly disturbed schizophrenic (and bipolar) patients memory deficits have been associated with skills that affect encoding and are, perhaps, secondary to a cortical attention and executive dysfunction as these groups show different recall patterns to the severely disturbed whose memory impairment may be more fundamental (Calev et al, 1983; Levin et al, 1989).

1.5.1 Memory, medication and hospitalisation (see also subsection 'Neuroleptic effects on memory and learning')

Though it may appear that memory difficulties may be characteristic of groups of schizophrenic patients in various stages and states of the illness, it has been disputed whether the deficits shown are due to the process(es) of the disease alone or are affected by variables such as medication and/or the effects of long term hospitalisation.

Sweeney et al (1991) reported that neuroleptics and anticholinergics are associated with poor verbal recognition memory as far as schizophrenia is concerned. The effects of the medication were seen to be influenced by higher doses. Spohn and Strauss (1989) associated neuroleptic medication with limited 'normalisation' on a broad range of psychological tests and anticholinergics, particularly, with apparent disruption of some aspects of memory.

Calev et al (1991) tested a group of 8 long stay hospitalised chronic schizophrenic patients who had been withdrawn from both neuroleptic and anticholinergic medication. Their medication was reduced to zero levels over two weeks and the subjects were left drug free for four weeks before testing began. The patients were tested on Calev et al's (1983) immediate and delayed matched recall tasks for measurement of their rate of forgetting of well encoded verbal material. The results showed rapid forgetting in the schizophrenic patient group (compared to controls). The authors proposed a post encoding deficit responsible for the poor performance. The retrieval difficulties observed could have been due to the disruption of any meaningful organisation of the materials to be remembered. Such disruption has been observed in amnesic groups displaying signs of hippocampal and temporal lobe dysfunction (Squire 1986; 1987), therefore, similar brain pathology may be responsible for the memory deficits seen in groups of long term severely disturbed chronic schizophrenic patients.

There is an important problem, however, associated with the interpretation of the above results from such a drug free sample. Although the evidence is scant, the effects could, in part, be due to the irreversible effects of long term medication. Also, one must question whether the effects are due to the actual process of withdrawal from the medication in the

first place. Another confounding variable, which may have a significant affect on functioning, is that of the duration of hospitalisation and, therefore, the factor of institutionalisation arises. However important these observations are, contemporary evidence tends to support the hypothesis that significant impairment in memory functioning of schizophrenic patients exists that is due to the more than the sum of effects of institutionalisation and withdrawal effects on their own (Calev et al, 1991; see also McKenna et al, 1990, Saykin et al., 1991).

In summary, a consensus seems to be appearing associating poor performance on tests of long term memory (verbal and non-verbal) in various groups of schizophrenic patients, some studies showing a disproportionate deficit over other areas of cognitve impairment. There also seems to be marked deficits in the recall/retrieval of material over recognition. These observations have also been noted when medication and institutionalisation effects have been considered. Present evidence, however, has yet to determine a profile of memory impairment characteristic of groups of schizophrenic patients. More importantly, because of the heterogeneous nature of such groups evidence is even more lacking in associating specific memory deficits to the expression of particular symptoms. Optimistically, researchers are beginning to address these questions, in earnest, in order to contextualise the emerging memory deficits within more complex models of psychological dysfunction which give rise to particular schizophrenic symptoms.

1.6 Lateralization studies and schizophrenia

It has been suggested that the cognitve dysfunction associated with memory dysfunction, at least, implicates bilateral impairment in schizophrenia (Calev et al., 1991). However, this has only sought to exaggerate the amibiguity surrounding the question whether the pathophysiology responsible for schizophrenic symptoms is hemisphere specific (Cororan and Frith, 1993). Left hemispheric dysfunction has been popularly presented as characterising a relative hemispheric imbalance in functioning in schizophrenia (Gur, 1978). Left turning bias or circling behaviour associated with right hemispatial neglect (i.e. left hemispheric dysfunction) has been widely reported in groups of schizophrenic patients in recent years (Bracha, 1987; Lyon and Satz, 1991) with unmedicated and medicated subjects respectively. This specific behaviour, particularly in animal studies, has been related to asymmetry in dopaminergic activity between the left and right basal ganglia and the left and right frontal cortex (Glick and Ross, 1981; Stewart et al, 1985). In more recent times it has been suggested that the presence of dopaminergic activity in unmedicated patients, at least, reflects right anterior subcortical or cortical structures manifesting a *relative* dopaminergic overactivity compared to the left anterior structures (Bracha, 1987). Schizophrenic patients have also been observed demonstrating deficits in attention reflective of patients with unilateral lesions of the left hemisphere (Posner et al, 1988).

Tomer and Flor-Henry (1989) found attention asymmetry clearly related to the medication status of the patient. Unmedicated schizophrenic patients would show inattention to the right visual field (right hemispatial neglect expressed by left turning bias behaviour) which changed to more prominent left sided inattention after medication. This

'shift' was associated with longer duration or higher daily dose of medication. All in all, this appears suggestive that medication helps normalise left hemisphere performance whilst deterioration of right side performance occurs, as the 'shift' did not herald a difference in the level of functioning only the nature. Therefore, evidence of lateralization of dysfunction appears to be affected by medication, which should be considered in future studies. This may also help determine dopaminergic innervation of arousal in each hemisphere responsible for the emerging pattern of neuropsychological functioning associated with schizophrenic symptoms.

In terms of symptom expression, positive thought disorder has been associated with speech and language dysfunction in the left hemisphere, but negative thought disorder has been attributed to more bilateral damage (Silverstein et al., 1991). However, Cutting (1994) suggests that right parietal damage has been associated with experiencing one's voice as alien. Thus contemporary evidence for a specific hemispherical dysfunction in schizophrenia is far from conclusive. Future studies ought to clarify the association of hemispheric differences in terms of specific symptoms. Also, care ought to be taken in attributing hemispherical dysfunction to certain patterns of neuropsychological performance as many tests involve multiple processes and thus more interactive, including interhemispheric, brain systems.

1.7 Drug treatment, Neuropsychology and Schizophrenia

The two main reasons why neuroleptics are prescribed are for the effective reduction or removal of acute symptoms and the prevention of relapse in those recovered from an episode. There are three major groups of standard neuroleptics; the phenothiazines, the

butyrophones and the thioxanthenes. These drugs are limited in their usage as they are not effective for all, can generate serious side effects and are restricted to the kinds of symptoms they can actually ameliorate. However, when a drug is chosen, consideration is given to the patients pharmacological history, and their particular response. There are, however, no particular individual characteristics of a patient that can reliably predict their response to a particular drug (Goldberg et al, 1972).

The potency of standard neuroleptics e.g. phenothiazines correlates well with its affinity for the postsynaptic D2 receptor (Tune et al, 1980). Although low doses appear less able to effect clinical response, there is evidence that high doses may exacerbate symptoms and reveal cognitive dysfunction (Spohn et al, 1985 -see later). However, all neuroleptics show varying and diverse side effects. The high potency drugs eg. haloperidol and fluphenazine seem to cause less sedation, few anticholinergic effects (eg. tachychardia) but are responsible for producing more extrapyramidal side effects (eg. drug induced Parkinsonism, akathisia and tardive dyskinesia). Thus the particular group of side effects assumed least harmful would be of importance clinically when choosing a drug suitable for an individual. Although high potency drugs seem to be favoured clinically (and at higher doses) over low potency drugs, as they are seen as better tolerated by the individual patient, the concomitant side effects usually necessitate compensatory medicine ie. anticholinergics. Anticholinergics are primarily prescribed for the management of extrapyramidal side effects ie. pseudoparkinsonism, dystonia, akathisia. Johnson (1978) observed that approximately 10% of patients' extrapyramidal side effects reappear on discontinuation of their anticholinergic medication. Such medication can also manage depressive symptoms concomitant to the primary disease (Johnson, 1981). The

disadvantages of anticholinergics are discussed later with particular reference to cognitive abilities.

The question of appropriate dosage has not, as yet, been absolutely answered. The advocation of 'rapid neuroleptization' (Donlon and Tupin, 1974)- the acutely psychotic receiving frequent doses of high potency drugs until overt sedation occurred- was proposed at one time. Van Putten et al (1987) has addressed the subject of optimal dose and observed that 20mg (haloperidol) resulted in significantly more improvement (as measured by the BPRS) than 5mg, but held only a marginal advantage over 10mg per day. Patients on 20mg showed greater deterioration in blunted affect, emotional withdrawal and motor retardation amongst other symptoms. As a caveat, therefore, it is necessary to see the high dosage advantages in context of the obvious toxic effects. Baldessarini et al (1988) reported that no additional benefit is likely with doses above 600mg chlorpromazine (CPZ) equivalent (approx. 12mg haloperidol)- there is, in fact, a slight trend towards decreasing efficacy above 600mg CPZ equivalent. The same decreased efficacy was observed when the dose went below 250mg CPZ equivalent when compared to mid range doses. Thus, there appears a curvilinear relation existing between dose and response.

1.7.1 Treatment of neuroleptic-unresponsive schizophrenia

A small but significant proportion, approximately 10-20%, of schizophrenic patients derive little benefit from typical neuroleptic administration (Davis et al, 1980; Friedhoff, 1983). Six to eight per cent essentially show no response from the beginning of their illness (Tuma and May, 1979; McMillan et al., 1986). However, there are, as yet, no clear

predictors who will comprise this group (Kane, 1987), although chronic hospitalised patients are predominantly these kind of sufferers.

Reports have supported the use of very high doses in the management of treatment resistant populations (Rifkin et al, 1971). Qitkin et al (1975) suggested that reported results favour 'standard' rather than 'megadoses'of neuroleptics. This assumes high doses would only benefit a small proportion of treatment-resistant schizophrenic patients. Small et al (1975) showed that adding lithium therapy to standard neuroleptic administration reduced symptomatology in a chronically hospitalised and, relatively, treatment-resistant group.

A source of optimism for the treatment of patients unresponsive to standard neuroleptic medication has been the development of atypical neuroleptics such as clozapine and risperidone. These drugs have different psychopharmacological properties to the standard dopamine antagonists such as chlorpromazine. Clozapine has a weak affinity for dopamine receptors but possesses powerful blocking effects for serotinergic receptors. Risperidone has both potent serotinergic (S2) and dopaminergic (D2) blocking properties. Both clozapine and risperidone have had significant ameliorating effects on symptoms with patients unresponsive to haloperidol (Kane et al., 1988; Marder and Meibach, 1994).

1.7.2 Long term strategies; maintenance and management.

The symptom reducing effects of neuroleptics are dependent on continuous treatment. If drug therapy is discontinued, on average, 40% of patients relapse within 6 months and

70% within one year (Hogarty et al, 1973). Long term maintenance substantially reduces such relapse rates but is also associated with serious neurological side effects eg. tardive dyskinesia. If, therefore, discontinuation is unfeasible, the only realistic strategy for reducing tardive dyskinesia is management via the lowest effective dose. This point is extremely important as tardive dyskinesia has been associated with both cognitive and psychophysiological problems in schizophrenia (Waddington, 1987). Another advantage of low dose maintenance is that the extrapyramidal side effects have the potential for lowering the mood of the patient. According to Spohn and Strauss (1989) two strategies exist for the investigation of this effect;

a) Treating patients intermittently with maintenance drugs, on a gradual decrease, until signs of relapse are evident, then the drug is reinstituted. Not only is close clinical supervision of the utmost importance, in this strategy, but also family training is necessary for the detection of the first signs of relapse. Jolley et al (1989) argued that patients here are more likely to suffer recurrence of their psychotic symptoms.

b) The 'dose reduction' strategy involves doses administered at lower levels than usually prescribed. Kane et al (1983) reported that relapse rates on these lower levels were significantly lower than on placebo and that patients had better outcomes on measurements of social adjustment and dyskinesia ratings. Marder et al (1984, 1987) suggested that lowering the doses, substantially in well stabilised patients is relatively safe if the clinician is sensitive to a worsening condition to make an appropriate dose adjustment. Dosage reduction reduces the likelihood of side effects and extremely few reports of anxiety or depressive symptoms have been recorded (Marder et al, 1991). Compliance seems to increase the advantage. However, the results of such strategies

ought not to be generalised to whole populations as most studies rely on well-stabilised populations of schizophrenics.

In summary, neuroleptics have been a therapeutic leap forward for the reduction of acute symptoms and prevention of relapse in chronically occurring schizophrenia. However, drugs of this nature are limited in their usefulness by the concomitant side effects. Drugs, in themselves, presently provide little optimism for cure and most patients will continue to display schizophrenic symptoms to one degree or another despite their drug regime. However, with the development of new atypical neuroleptics some hope of relief and effective management is beginning to be available for a proportion of the schizophrenic population who had previously been impervious to the effects of medication.

1.7.3 Drugs, behaviour and schizophrenia.

The heterogeneity of symptom expression in groups of schizophrenic patients and individual demographics i.e. chronicity and duration and type of medication, pose a major problem for the interpretation of the literature concerned with the relationship between drug effects and behaviour. Spohn and Strauss (1989) proposed two general methodological considerations for investigations in this field. Firstly, the demonstration or dismissal of 'direct effects' is problematic. Drug manipulation exercises are always mediated by clinical judgement before any interpretation of psychological functioning takes place. It is, therefore, almost impossible to determine cause and effect relationships in this way. Secondly, clinical efficacy scales do not require patient cooperation. Studies of drug effects on psychological functioning require the willingness to participate. Relapsed patients are untestable. Testing, therefore, cannot avoid a form of selection bias.

1.7.4 Designs used in drug-behaviour studies.

Common methodologies include:

a) Comparison of an 'on drug' population to an 'off drug' population. There is the problem that group differences cannot definitely be attributable to medication effects. Long term residual side effects of previous medication and hospitalisation factors could affect inferences here.

b) Comparison of the same group at the end of 'washout' and after a period of resumption.

c) A counterbalanced or crossover design, where patients serve as controls-one subgroup tested on drug then off. Another subgroup is tested obversely, all under double blind conditions. Problems accrue when drug influence may carry itself over into the off drug phase. At least, a three week washout, between on and off drug stages, should negate this influence (Spohn and Strauss, 1989).

d) The independent group placebo controlled design (patients are randomised to an on drug or placebo condition-under double blind conditions). The groups are then tested over a period to allow the neuroleptic to take full effect. This design can differentiated in light of traditional schizophrenic subclassification;

i) acute treatment-patients are randomised whilst in an acute episode;

ii) chronic sufferers are withdrawn from their standard medication, washed out and then randomised- this is known as a 'discontinuation design'.

1.7.5 Neuroleptics and effects on cognitive functioning in schizophrenia.

In a recent review Cassens et al (1990) concluded that the effect of neuroleptics on cognitive, perceptual and motor behaviour has remained ambiguously defined throughout the literature. Although the area has far from been ignored, unfortunately, it has been characterised by contradiction. On a more progressive note, there is a desirability for order in this area due to the present increased interest in the aetiological and prognostic significance of neuropsychological abnormalities in schizophrenia. In addition, there is also a need to differentiate such abnormalities from drug effects. The knowledge of drug effects on cognition, of course, may clarify those neural regions and transmitter systems primarily involved in the expression of schizophrenic behaviour.

1.7.5.1 Reviews of drug effects on cognition in schizophrenia

Spohn and Strauss (1989) concluded that neuroleptic administration was associated with a significant degree of 'normalisation' of disordered thinking and attention/general information processing, although this normalisation was not directly related to clinincal improvement. Cassens et al. (1990), reviewing neuropsychological test peformance and medication effects, observed that acute administration impaired some but not all tasks requiring vigilance/attention and some motor skills. Improvement could be seen, after chronic administration, on tasks of sustained attention and visuospatial problem solving, less so at high doses. Saletu et al. (1986) found that chronic administration of haloperidol and flurperlapine improved 75% of a range of neuropsychological test performances, although acute administration compromised performance. Heaton and Crowley (1981) concluded that very few changes of neuropsychological functioning occur after chronic continuous neuroleptic administration. These reviews reinforce the ambiguous state of drug-cognition relations in schizophrenic research. Despite these reviews specific areas of functioning have been investigated in an attempt to clarify the effects of neuroleptics on cognition which provide a more detailed appreciation of the field.

1.7.5.2 Neuroleptic effects on intelligence.

Pearl (1962) observed no *general* improvement in intellectual functioning associated with neuroleptic administration. Improvement was observed, solely, on performance of the subtest 'similarities' (WAIS and Wechsler-Bellvue batteries). Although the author thought this improvement might have been due to chance, it is, interesting to note that performance on 'similarities' subtest can be considered as sensitive to idiosyncratic

thinking or thought disorder and, thus, corroborates the theory that neuroleptics can ameliorate this type of thinking. Although Gorham (1956) had reported significantly more examples of concrete thinking in schizophrenic patients than normals, Shimkunas et al (1966) found no change in measures of abstract and concrete thinking over a 5 week neuroleptic treatment period. Shimkunas et al (1966) proposed that verbal IQ accounts for more of the variance observed, than the ratings of severe psychopathology, in measures of concrete thinking. Harrow et al (1977) supported this conclusion and suggested that intelligence was the most powerful influence on abstract or concrete thinking despite medication.

1.7.5.3 Neuroleptic effects on measures of attention and vigilance.

Daston (1959) reported that chronic schizophrenic patients on chlorpromazine showed particular improvement in tests of 'immediate memory' or 'span of concentrative attention'. Concentrative attention (sustained attention or vigilance) has been gauged widely by the use of the Continuous Performance Test (CPT) (Rosvold et al, 1956). The test yields error of omission or commission scores (ie failure to respond to a target, usually a letter, occurring randomly among a continuous presentation of non-targets or responding to non-target letters), perceptual sensitivity is judged to be derived from the raw scores. Orzack and Kornetsky (1966) found that schizophrenic patients were significantly more impaired on the CPT than alcoholics or normals (no difference was observed between schizophrenic patients and normals on a digit symbol substitution test). Orzack et al (1967), in a study of hospitalised chronic schizophrenic patients, off medication one month prior to testing and then treated with phenothiazines and then tested after a period of 12 weeks, found a significant decrease in errors of omission on

the CPT and no change in the DSST scores. The improved performance on the CPT was positively correlated with clinical improvement. This result was replicated by Spohn et al (1977). Such studies are, therefore, suggestive that an association exists linking neuroleptic treatment, clinical improvement and the 'normalisation' of sustained attention, particularly in samples of chronic schizophrenic patients. However, this observation may be restricted to certain functions and possibly not found with others. Pugh (1968) noted that no neuroleptic induced alteration of performance could be reported during trials using the Trail Making Test. Killian et al (1984) noted, in addition, that neuroleptics show no significant effect on Stroop Test scores; these tests putatively sensitive to frontal lobe functioning (Stroop, 1935; Reitan, 1958).

1.7.5.4 Neuroleptic effect and distractibility.

Oltmans et al (1978), using a digit span test (with and without a distractibility component) found, with a sample of chronic schizophrenic patients, that antipsychotic medication helped in the alleviation of the disrupting influence of the distracting stimuli. The decrease in distractibility was positively correlated with a reduction of thought disorder in the experimental group. Spohn et al (1985) also recorded a significant decrease in the influence of distracters on a digit span test after neuroleptic administration, compared to a control group. Strauss et al (1985) found that a decrease in distractibility was associated with higher serum neuroleptic levels.

1.7.5.5 Neuroleptic effect on visuospatial/visuomotor tasks.

Improvement has been observed, with chronic schizophrenic patients, after the administration of chlorpromazine on, at least, two subtests of the Wechsler Adult Intelligence Scale, allegedly sensitive to spatial ability, those of 'block design' and 'picture arrangement' (Small et al,1972). The authors used patients on 300mg/day of chlorpromazine for a period of 3-6 weeks. However, Abrams (1958) had reported no change when 400-600mg/day were administered over an 8 week period. Killian et al (1984) found similar results to Abrams but, unfortunately, did not specify the dose of neuroleptic used. It appears, then, that the dose level may be integral in determining any neuropsychological benefit as far as visuospatial skills are concerned. Although in any appreciation of WAIS scores are concerned (especially if improvement is observed) attention must be paid to potential practice effects after repeated administration.

1.7.5.6 Neuroleptic effect on memory and learning tasks (See also 'Memory and Schizophrenia').

There have, as yet, been relatively few studies on the effects of neuroleptics on memory tasks (Spohn and Strauss, 1989). However, this field is gaining increasing interest focusing, moreover, on the effects of anticholinergics on memory in schizophrenia (and, also, the particular anticholinergic properties of typical and atypical antipsychotics).

Daston (1959) found that 400mg/day of chlorpromazine enhanced paired associate learning on the Wechsler Memory Scale in a sample of 26 chronic schizophrenic patients, promazine, at the same dose, did not. A chlorpromazine dose of 1400mg/day, again,

resulted in no significant drug effects. However, this study's results could not be replicated by Pearl (1962) and thus the effect is in want of further research. Pearl (1962) also reported few benefits of neuroleptic administration for the ability to retain narrative stories or enhancing mental control, with groups of schizophrenic patients.

1.7.5.6.1 Anticholinergic effects on memory.

Frith (1984) proposed that the memory impairment observed with many schizophrenic patients maybe consequential to treatment with anticholinergics (drugs given to combat the side effects of the neuroleptics). Such an assumption was based on neuropathological evidence associating the loss of acetylcholine secreting neurones with the onset of dementia with its characteristic impairment of memory (against a backdrop of global intellectual decline) (Deutsch, 1983). In a review, Drachman (1977) suggested there is widening evidence to support an instrumental role for anticholinergics in the impairment of memory observed in schizophrenic patient populations. Tune et al (1982) found a significant inverse correlation between word list recall and serum levels of anticholinergics such that serum levels were associated with poor performance. This was confirmed by Perlick et al (1986) using radioreceptor assays. Research has also arisen implicating benzodiazepines in affecting memory similarly to that associated with anticholinergics (Frith et al, 1984). However, the effect is probably not mediated, in this instance, by the cholinergic system (Ghoreim and Mewdalt, 1975).

In a slightly different study, Eitan et al (1992) compared the effects of four antipsychotics possessing varying anticholinergic properties on various memory tasks. They found that chlorpromazine and thioridazine impaired functioning on measures of verbal short term

memory (after 6 hours sequential administration). Trifluoperazine and haloperidol improved verbal STM from the 3rd to the 5th administration. Immediate memory, long term memory and visual short term memory were unaffected by any drug. It is interesting to note that deterioration effects were only noticeable after the cumulative administration of the drugs responsible. Therefore, the effect of such drugs on memory functioning may well be dependent on the duration of administration. These results appear to support previous findings i.e. the more potent the anticholinergic properties of the drug the greater the memory impairment. Fennig et al (1986) showed that the anticholinergic trihexyphenidyl did not impair immediate memory in schizophrenic patients but did impair STM and LTM functions. It can be hypothesised, therefore, that anticholinergics do play a key role in the memory deterioration observed in schizophrenic patinets receiving such medication. Spohn and Strauss (1989) beg caution by imploring further research to explain the individuality of results since, even in the Eitan et al (1992) report, the drugs in question did not affect short term visual memory or long term memory functions.

Research into the effects of anticholinergic medication on memory functioning has been complicated since recent evidence points to a distinct memory impairment with various groups of schizophrenic patients, even when medication free or drug naive (Saykin et al., 1991;1994). Thus, in turn, any investigation into memory impairment in schizophrenia should account for anticholinergic administration.

1.7.5.7 Atypical neuroleptics and cognition

In one of the few studies to date, concerning the effects of the new antipsychotic neuroleptics on cognitive performance, Goldberg et al. (1993) found that

neuropsychological performance did not significantly improve, despite significant symptom improvement, from testing when on standard neuroleptics and 15 months duration on clozapine. The levels of performance were well below the norm at either point. The authors suggested this pattern reflected a fundamental neuropsychological impairment in schizophrenia that, although here independent of symptom expression, probably accounted for much of the social and occupational dysfucntion seen in their sample.

1.7.5.8 Future studies.

From the increasing body of knowledge of the various ameliorating effects of neuroleptics on symptoms, it may be logical to assume a concomitant improvement in neuropsychological functioning in groups of schizophrenic patients. However, the present state of this research reveals a complex and contradictory state of affairs. In line with Cassens et al. (1990), this area of research will only become clearer when studies unambiguously compare specific areas of neuropsychological functioning with symptom expression in controlled drug trials involving neuroleptics with known biochemical activity. The advent of the atypical neuroleptics may offer an opportunity to enhance knowledge of the neurochemical substrates involved in symptom expression, while parallel neuropsychological investigations may clarify the mediation of putative brain dysfunction that results in particular symptoms of schizophrenia.

1.8 General Aims of the Studies reported in this Thesis.

1) To assess the relationship between empirically related signs/symptoms of schizophrenia and neuropsychological performance across both acute and chronic phases of illness.

2) To investigate the relationship between typical and atypical neuroleptic medication, symptom expression and neuropsychological functioning with treatment resistant schizophrenic patients.

3) To assess the neuropsychological functioning profiles of schizophrenic patients dichotomised by clinical, and social outcome status to determine the neuropsychological correlates of good and poor outcome in schizophrenia.

CHAPTER 2: METHODS

THE NEUROPSYCHOLOGICAL TEST BATTERY USED IN THE STUDY OF THE NEUROPSYCHOLOGY OF SCHIZOPHRENIA, SYMPTOMS AND MEDICATION

2.1 What is the purpose of neuropsychological assessment?

Muriel Lezak (1983) stated that, '...to do justice to a field of inquiry as complex as brain-behaviour relationships ...an adaptable assessment methodology that incorporates the strengths of both quantitative and qualitative approaches is required. Standardized procedures [i.e. psychometric testing] provide objectivity and the potential to make fine distinctions and comparisons which would be unattainable by clinical observation alone (p.4)'. However, she admonished that comprehensive knowledge of the subject/patient background is also required as behaviour is psychologically and socially contextual. More specifically, the author defines the area of clinical neuropsychology as an applied science concerned with the behavioural sequelae of brain dysfunction. The purpose of such investigations is to identify, assess and aid rehabilitation of brain injured patients. Serial testing may gauge the course of an underlying neurological condition and may assess intervention procedures such as drug therapy or training over time (Lezak, 1983).

2.1.1 Neuropsychological assessment and Schizophrenia

As schizophrenia is a condition characterized by abnormal perceptions and expressions of abnormal behaviour, researchers have turned to neuropsychological methodology to try to explain the defining symptoms in terms of abnormal psychological processes. Neuropsychologists such as Gray et al. (1991) and Frith (1992) (see Introduction) have tried to provide comprehensive and testable theories of information processing abnormalities that underlie various schizophrenic symptoms. This field of investigation has its foundations in neuropsychological studies of brain-damaged individuals, which provide important information concerning the cognitive processes involved in 'normal' functioning. This 'cognitive neuropsychological' approach is deemed suitable for the investigation of schizophrenic behaviour as it may give clear indications to the nature of the key underlying cognitive abnormalities associated with particular signs and symptoms schizophrenia.

Therefore, the neuropsychological approach used in the present study involved administering a battery of specific psychometric instruments, the content of which has been dictated by theoretical considerations and behavioural characteristics associated with the study group(s) i.e. schizophrenic patients. The object of such testing was to provide a profile of neuropsychological functioning for the study group(s) and to relate any emergent patterns with symptom ratings. In this way we may be able to discriminate particular neuropsychological functions/modalities associated with specific signs/symptoms of schizophrenic behaviour.

2.2 DESCRIPTION OF THE NEUROPSYCHOLOGICAL MEASURES USED IN THE PRESENT STUDIES

2.2.1 MEASURES OF GENERAL INTELLECTUAL ABILITY

2.2.1.1 Pre morbid Indices

Pre morbid indices are essential in improving the detection and quantification of impairment [of functioning] by providing an individualized standard against which contemporary performance may be compared (Crawford, 1992).

Nelson (1982) points out that background demographic data e.g. occupation or education, give only a crude appraisal of the pre morbid intellectual functioning of an individual. Assessing ability in terms of the complexity and demands of one particular job against another, in terms of intellectual ability, is not easily quantifiable and is confounded by variations in social class highlighting social advantage. Similarly, for education background, opportunity and differences in matriculation standards across age groups does not readily proffer reliable indications of pre morbid ability-to be compared with present functioning-assessed on standardized measures.

2.2.1.1.1 The National Adult Reading Test (NART) (Nelson and O'Connell, 1978; Nelson, 1982).

Background

Nelson and McKenna (1975) demonstrated a significant correlation between word reading ability and general intelligence in a group of normal adults. Results from a group of dementing patients showed that reading ability was relatively well maintained in the face of significant impairment in other cognitive functions. The National Adult Reading Test (NART; Nelson and O'Connell, 1978; Nelson, 1982) was, therefore, developed incorporating words enabling reliable discrimination along a wide spectrum of intellectual abilities. Thus the NART was designed to provide an estimate of pre morbid intellectual ability, based on word reading ability, of adult patients demonstrating signs of current intellectual deterioration.

Description of the NART

The NART is a single word oral reading test. It comprises of 50 irregular words not following normal grapheme-phoneme correspondence e.g. 'Depot'. The words are short, therefore no complex visual analysis is required and, because they are irregular, guesswork will be unsuccessful. A successful test performance, therefore, requires previous familiarity with the words and makes minimal demands on current cognitive capacity (Nelson and O'Connell, 1978).

That the NART is a valid and reliable measure of pre morbid intellectual functioning is based on the following assumptions (Crawford, 1992);

a) The pronunciation of irregular words is unaffected in various clinical (neuropathological) disorders.

b) NART performance is highly correlated with general intellectual ability.

Reliability of the NART

The NART has been highlighted as one of the most reliable psychometric tests used in present clinical practice (Crawford, 1989). It has excellent inter-rater and test/retest reliability (Crawford et al, 1989b; O'Carroll et al, 1987).

Validity of the NART

Crawford et al (1989b) examining Nelson's (1982) original standardization sample reported that the NART predicted 55%, 60% and 32% of the variance in WAIS Full Scale, Verbal and Performance IQ respectively. They concluded that the NART has high construct validity as a measure of general ability and is a powerful predictor of WAIS Full Scale IQ, Verbal IQ but relatively poor at predicting Performance IQ. In addition, NART performance has shown to be intact despite the presence of dementia (Sharpe and O'Carroll, 1991).

NART Performance in Neurological and Psychiatric disorders

Nelson and O'Connell (1978) reported that, after an investigation involving MRI scanning, NART performance was unaffected by the presence of cortical atrophy. O'Carroll et al. (1987), in a longitudinal study of patients with dementia, retested their sample on the NART after one year. Although dementia severity and physical disability had worsened significantly in the intervening period, NART performance had remained constant. In general, Crawford (1992) suggests that NART performance shows a relative resistance to a wide range of neurological disorders.

Crawford (1992) provides a caveat for the usage and interpretation of the NART. Firstly, NART should not be used with groups of dyslexic patients or with clients exhibiting obvious articulatory problems. In addition, as a methodological issue, the author advises caution in assuming that performance on any measure of current ability would be entirely unaffected by severe cerebral dysfunction. Some studies have indeed shown deterioration in NART performance, particularly with Huntington's patients (Crawford et al., 1988) and Korsakoff's Psychosis patients (Crawford et al., 1988; O'Carroll et al., 1992). Patterson et al. (1994) found that NART scores might underestimate pre morbid intellectual functioning by up to 15 IQ points with patients suffering only moderate dementia. These results caution against the indescriminant usage of the NART, as a pre morbid index of intellectual functioning, with all groups and severities of mental illness or pathological brain disorders. To overcome some of

the methodological problems associated with the NART, O'Carroll (1995) suggests that placing NART words in context in meaningful sentences may provide a more accurate estimate of premorbid functioning. This type of test requires lexical decision-making competency and avoids problems associated with pronunciation based formats. In addition, this type of test may be more sensitive to those patients who are familiar with the word and its meaning but are unsure as to its pronuciation.

NART Performance and Schizophrenia

When acute unmedicated schizophrenic patients were compared with a group of acutely ill unmedicated patients suffering other forms of psychosis and a group of healthy controls, no difference in NART performance was recorded between all three groups (O'Carroll et al, 1992). The acutely ill schizophrenic patients did, however, show a significant deterioration in functioning between NART performance and current intellectual ability. In conclusion, the NART was seen as a reasonable estimate of pre morbid ability for patients at this stage of their illness. However, Crawford et al. (1992) reported that, although NART performance did not differ between community based schizophrenic patients and matched controls, there was a significant disparity in functioning between a group of long term hospitalized schizophrenic patients and their matched controls. Thus, within the latter group of patients, interpreting NART performance poses a problem. Although poor performance may highlight genuine low levels of pre morbid intellectual functioning, performance may also have been affected by the disease process itself and/or the effects of long term

treatment and institutionalisation. If the disease process results in poor NART performance, the use of the NART as an index of 'pure' pre morbid ability in this group must be called into question. Such observations warrant caution in the usage of the NART with such groups of more chronically ill schizophrenic patients. Jones and Rodgers (1993) provided alternative explanations for the low NART scores in the long term hospitalised sample to that of the putative influence of the disease process in this group. Firstly, the lack of other long term hospitalized psychiatric patients in the control group did not address the effects of long term stay and long term exposure to psychotropic medication, independent of illness, on performance. Secondly, studies showing an appreciable continuation of acquired reading skills into later life in the general population (Rodgers, 1986) might also provide an alternative account for the difference in NART performance here. Although the long term schizophrenic patients showed a poorer NART performance it could be due to the disease affecting later reading skill acquisition compared to healthy controls rather than any disease effect on pre morbid reading skill acquisition. The authors did admit, however, that it would be unwise to ignore the possible difficulties inherent in using NART error scores in providing distinct pre morbid IQ levels for long term hospitalised groups where a combination of factors may yield poor performance. However, they concluded that, on balance, with the obvious cautions, the NART is probably a more accurate assessment of pre morbid intellectual functioning in schizophrenia than is presently provided by any alternative methods.

Administration (The NART was administered according to the NART manual (Nelson, 1982).

Scoring

An error score was calculated for each word mispronounced. A WAIS conversion table was used to equate NART errors with a 'predicted' Full Scale IQ score. [NB A WAIS rather than WAIS-R table was used as the measure assessing current IQ- the Quick IQ -is based on WAIS equivalent scores.]

2.2.1.2 Measures of Current Intellectual Performance

2.2.1.2.1 The Quick Test (Ammons and Ammons, 1962).

The Quick Test (QT) was chosen as a relatively easily administered 'quick' test to assess current intellectual functioning in terms of verbal picture recognition ability. Although comprehensive measures of global intellectual functioning exist (e.g. WAIS-R (Wechsler, 1981)) administration time is approximately 1.5-2 hours. As the object of the present studies was to assess schizophrenic performance on tests measuring a wide range of specific cognitive abilities, the use of protracted measures of global intellectual functioning was deemed impractical. The use of complex and time consuming global measures of intellectual functioning, therefore, seemed unnecessary especially in the light of the restricted attention and cooperation one could expect from groups of severely disturbed individuals.

Background

The Quick Test was developed from the Full Range Picture Vocabulary Test (FRPV) (Ammons and Huth, 1949) to reflect the following characteristics: brief (to save time and to make possible the testing of persons with very short attention spans); covering the full range of abilities; suitable for examining the severely brain-injured and physically handicapped, both children and adults; of sufficient reliability and validity to justify making important diagnostic and training decisions on the basis of its scores (Ammons and Ammons, 1962). This type of test makes use of pictorial representations among which the testee chooses one which best illustrates the concept suggested by the examiner i.e. the word 'sweet' would be associated with the picture of a drink rather than pictures of a race track, people dancing or a policeman. The authors suggest that both the FRPV and QT tap a very fundamental behavioural process, the visual-perceptual recognition of basic concepts utilized in language, and, therefore, in a great deal of thinking.

Description of the QT

The Quick Test is seen as a verbal-perceptual test of [current] intelligence. It comprises simple black and white line drawings among which the testee chooses the ones that best illustrate a variety of concepts, thus obtaining responses that are easy to interpret and score objectively.

Reliability and Validity of the QT

The FRPV, on which the QT is modelled showed a .80 test-retest reliability with a group of 48 aphasic patients (Shuell et al, 1961). As far as validity goes, a correlation of .86 was recorded between the FRPV and the Wechsler-Bellevue Vocabulary with 69 deteriorated schizophrenic patients (Blatt, 1959). Ammons and Ammons (1962) suggested such reliability and validity should, therefore, apply to the use of the Quick Test. The authors provided a large database of reliability studies for the QT. The authors suggested that the evidence demonstrates that single forms of the QT are likely to be suitable for screening of intelligence at single age levels and very effective where wider ranges of ability are being handled, as in clinical populations. Frith et al. (1991) found a high correlation of performance between the WAIS and the Quick Test with nine chronic schizophrenic patients (mean (sd) WAIS 83.6 (17.3), Quick 78.7 (19.2); r (Quick, WAIS=0.91).

As far as validation of the QT is concerned, Ammons and Ammons (1962) pointed to the high correlational relationships between the QT the FRPV and 'longer' intelligence tests of more heterogenous content. QT scores significantly correlated with percentile scores in a number of areas on the Iowa Test of Basic Skills (Lindquist and Hieronymous, 1955) and with school grades in several subjects.

The Quick Test and Schizophrenia

The Quick Test has been used previously to estimate current IQ in groups of schizophrenic patients (Gessler et al., 1989). Some evidence of its validity was shown in that there was no discrepancy in IQs assessed by the Quick and the NART in the normal control group. However, there was a 12.8 discrepancy between pre morbid and current measures in their group of chronic schizophrenic patients, as might be expected. Frith et al (1991) tested a sample of 283 schizophrenic patients on theses measures of intellectual functioning. Pre morbid functioning was similar to control data. There was, however, a substantial decline in IQ (Quick scores) similar to that observed by Nelson et al (1990) and Gessler et al (1989), the former group using the WAIS-R (Wechsler, 1981).

Administration

Form A of the Quick was administered according to the test manual (Ammons and Ammons, 1962). Testing proceeded with all 50 items or until six words were failed consecutively (the Ss having previously passed at least six easier words).

Scoring

The QT scoring was objective and simple. The testee was given credit for each item correctly answered and for no item incorrectly answered. Separate percentiles and Wechsler-type IQ norms were provided for adults based on the assumption of a mean of 100 and a standard deviation of 15 IQ points. It was possible, therefore, to calculate an IQ score for each S based on WAIS equivalents.

2.2.1.2.2 The Mini Mental State Examination (MMSE) (Folstein et al, 1975; Dick et al, 1984).

This test was designed to assess global cognitive functioning simply and quickly. It has no abstract items but includes a diagnostically valuable verbal retention test (Lezak, 1983). Full details of the individual questions can be seen in the Appendices. The examination essentially deals with orientation, simple memory performance, mental control (backward serial sevens) and several verbal and non-verbal copying tasks.

MMSE administration takes approximately 5 to 10 mins.

Sixty three elderly healthy normals comprised the standardised population (mean age: 73.9). With a maximum score of 30, the controls (and a younger group of patients with 'functional' psychiatric disorders achieved scores in the 24.6-27.6

range. The scores of several groups of 'senile' (dementing) patients ranged from 9.6-12.2. There was no overlap between these patients and controls (Folstein et al., 1975). Dick et al (1984) suggest a score of 23 or less is indicative of cognitive impairment. This cut off point was derived from comparisons with significantly impaired WAIS IQ performance. Finally, the authors warn that the MMSE is relatively insensitive to right hemisphere damage on account of the high verbal content of the test.

2.2.3 MEASURES OF EXECUTIVE FUNCTIONING.

Lezak (1983) conceptualised 'executive functioning' as comprising four major components:

a) Goal formation

b) Planning

c) Carrying out goal-directed plans

d) 'Effective' [use of strategies in] performance.

The author suggested that the above are necessarily involved in 'appropriate, socially responsible and effectively self-serving conduct'. Executive functioning can breakdown at any point in the behavioural sequence that constitutes planned or intentional behaviour. Therefore, a systematic assessment of the capacities that enter into the above four aspects of executive functioning may help identify the stage(s) at which the dysfunction occurs.

Shallice (1988) proposed that executive or 'supervisory' functions are critical for the non-routine selection and control of cognitive processes. This supervisory system must have

access to the intentions of the individual and be involved in the 'supervision' of willed acts.

Patients with frontal lobe lesions appear to display disorganised and inappropriate behaviour that may be associated with impairment of executive functioning (Parker and Crawford, 1992) even in the face of intact IQ (Shallice and Burgess, 1991).

2.2.3.1 Executive functioning and Schizophrenia

Patterns of behaviour similar to those expressed by patients with frontal lobe pathology have been seen in groups of schizophrenic patients, particularly in relation to perseveration, disinhibition and negative symptoms e.g. psychomotor poverty, flattened affect and poverty of speech (see Introduction 1.3). Neuroimaging studies have provided evidence supporting a putative abnormality in the functioning of the frontal lobes in schizophrenia (Weinberger et al, 1986; 1988). As far as neuropsychological investigations are concerned, heterogeneous groups of schizophrenic patients have been seen to do particularly poorly on batteries of tests putatively sensitive to frontal lobe damage (Kolb and Wishaw, 1983; Gruzillier et al., 1988); this has also been shown in single case studies (Shallice et al, 1991), although not all patients showed the same performance profiles on such tests. Significantly poorer 'frontal'/ executive functioning performance has also been observed in comparison to performance on so-called non-frontal tests (Morrison-Stewart, 1992). Although, Braff et al. (1991) suggested 'frontal' problems, particularly on the Wisconsin Card Sort Test (WCST) (a measure of mental flexibility-see later) may be associated with a sub population of more deteriorated 'Kraepelian' patients. Saykin et al (1991) found that, with a group of unmedicated schizophrenic patients, though 'frontal' or

executive tests were poorly performed, there was significantly greater impairment in performance (relative to controls) on tests of memory and learning. Therefore, the emergent evidence suggests that impairment in executive functioning test performance may account for only part of a network of impaired cognitive modalities involved in schizophrenic behaviour and may be characteristic of particular stages of the illness. Frith (1992), however, warns that, although differing groups of neurological and psychiatric patients can exhibit similar behaviours clinically, they may not necessarily be indicative of the same underlying cognitive abnormalities. Therefore, whatever the degree of impairment, the putative executive functioning impairment of the schizophrenic patient ought to be assessed in its own right and preferably with respect to symptom profiles.

2.2.3.1 Verbal Fluency

Poverty of speech is a commonly observed 'negative' or residual symptom observed in schizophrenia (DSMIII-R, American Psychiatric Association, 1987). It has been explained in terms of an impairment of self-directed search (Frith, 1992).

The purpose of a verbal fluency test is to assess the spontaneous verbal production of words, beginning with a particular letter or of a given class, within a limited amount of time.

Background

Benton (1973) studied the ability to produce words by using a controlled word association test requiring the production of words according to an initial letter category,

in a limited time span, with a group of aphasic patients. Isaacs and Kennie (1973) used a variant of the word production test involving the recall of words in semantically distinct categories e.g. colours, animals, fruit, flowers as an aid to screening dementia in the elderly.

Description

In the present studies 'easy' letters (letters with a high frequency of occurrence in the English language) were used derived from the Thorndike and Lorge (1944) index of linguistic frequency i.e. an index of the frequency letters of the alphabet have to mean linguistic associations in the English language.

As a deterioration of intelligence (relative to pre morbid ability) has been associated with different groups of schizophrenic patients (Frith et al, 1991), easy letters were used in the projects' batteries as they may be more discriminating between schizophrenic patients and controls rather than using more obscure letters demanding greater 'cognitive effort'.

Verbal fluency was also measured in terms of words belonging to particular semantic categories e.g. animals. This 'Set Test' was developed by Isaacs and Kennie (1973) as a screening procedure for dementia.

The two ways of measuring verbal fluency were seen as different tasks according to the nature of the discrimination the Ss would have to use for correct word production. Word generation by initial letter requires the discrimination of words from non-words. Word generation by category, however, requires both discriminating words from non-words

and words from other words and provides a greater challenge to semantic memory systems. The two verbal fluency tasks together, therefore, give a comprehensive assessment of the Ss' ability to discriminate and select appropriate words for articulation.

Verbal fluency Studies

Borkowski et al (1967) found that for brain damaged patients with low intelligence 'easy' letters (e.g. F, A and S) were more effective in differentiating verbal fluency ability between brain damaged and control groups.

Scores for a mixed group of 200 aphasic adults ranged from 0-46 with a mean of 11.5; unselected brain damaged non-aphasic patients scores ranged from 5-46+ (mean: 28.2) (Spreen and Benton, 1977). Cavalli et al (1981) found no serious impairment with patients with right hemisphere lesions. Miceli et al (1981) observed a high sensitivity of performance on this test to frontal lobe damage regardless of the side of the lesion. However, Parks et al (1988) found more impairment for patients with left frontal lesions and Benton (1968) found the most severe impairment for patients with bilateral frontal lesions. Parks et al (1988) in a PET study using normal volunteers indicated that verbal fluency activated bilateral frontal and temporal lobes.

Reliability

Spreen and Strauss (1991) note that 'interscorer reliability [for the verbal fluency test] is near perfect'. One year retest reliability in older adults has been reported as high as .70 (Snow et al, 1988).

Verbal fluency and Schizophrenia

Groups of schizophrenic patients have been found to perform poorly on test of verbal fluency according to initial letter category (Kolb and Wishaw, 1983; Gruzelier et al, 1988) and on a semantic category (Gruzelier et al, 1988). Shallice et al. (1991), however, found that verbal fluency, in their small sample of five case studies, was performed relatively normally despite gross impairment on a range of other putatively frontal tests.

Administration (from Spreen and Strauss, 1991)

The Ss were required to produce as many words as possible within one minute for each of the categories. They were told to avoid recounting proper names e.g. Andrew and words with the same stem e.g. assess and assessing.

Test variations across studies

a) Risperidone trial (chronic treatment resistant patients): The letters A, W, D, H and the semantic category Animals were used individually for four different test sessions (i.e. a letter and the semantic category per session). The letters were chosen specifically to match for frequency of occurrence (from Thordike and Lorge (1944) index of linguistic frquency) to provide parallel versions for repeat testing.

b) Treatment resistant versus treatment responsive patients A and Animals.

c) Acute schizophrenic patient group: F, A, S and Animals.

d) Chronic schizophrenic patients: A and Animals.

e) Healthy controls: F, A, S and Animals.

These categories were in a sense arbitrary and composed to take into account the theoretical basis expounded above, the abilities of the individual groups and the overall construction of the individual test batteries undertaken for each study (see relevant chapter for further justification).

Scoring

The number of items correctly recalled in one minute was recorded. Proper names and words with the same stem were counted as incorrect.

2.2.3.2 Trail Making Test

This is a two part test of speed for visual search, attention, mental flexibility and motor function (Spreen and Strauss, 1991).

Originally, the Trails test comprised part of the Army Individual Test battery (1944) and was added to the Halstead-Reitan battery in 1958.

Des Rosiers and Kavanagh (1987) suggested that test loaded both on 'rapid visual search' and a 'visuo-spatial sequencing factor'.

Description

The test required the connection by making a continuous pencil line between 25 encircled numbers arranged on a page in proper order of increasing value (Part A) and 25 encircled numbers and letters in alternating order (Part B).

Reliability

The reliability of Part A remained high throughout 3 administrations to 19 normal controls at 6 and 12 month intervals (W(coefficient of concordance)=0.78). For Part B, reliability was somewhat lower (W=0.67) (Lezak, 1983).

Trail Making Test and Neurological Studies

Large differences between A and B have been interpreted as indicative of left lateralised lesions (Lewinsohn, 1973). More recent studies, however, have not confirmed this (Wedding, 1979).

Lezak (1983) suggested that slow times for both A and B point to the likelihood of brain damage, but do not indicate whether the underlying problem is one of motor slowing, coordination deficits, visual scanning difficulties, poor motivation or conceptual confusion. It is plainly obvious that performing the Trails test involves multiple brain systems i.e. speed, visual acuity, tracking and set shifting. Any interpretation of slow

times for the performance of this test must be made within the context of the complexity of the test.

Trail Making Performance and Schizophrenia

Shallice et al. (1991) found that in an intensive single case study report the 4 out of 5 of the sample were severely impaired on the numbers and letters form of the Trails test (Part B). Liddle and Morris (1991) found that this form of the test was highly correlated with their 'disorganisation' syndrome of symptoms after controlling for Part A (solely numbers).

Administration (see Spreen and Strauss, 1991)

Scoring

The time for Part A was subtracted from the time for completion of Part B to give a measure of attentional set switching, controlling for psychomotor speed.

2.2.3.3 The Stroop Test

The Stroop test is a test of focused attention in terms of operationalised visual search (Crawford et al, 1992). It measures the ease with which a person can shift perceptual set to conform to changing demands and suppress a habitual response in favour of an unusual one (Spreen and Strauss, 1991) or the ability to shift between conflicting response modes (Lezak, 1983).

Background

The test was first conceived by Stroop in 1935, after Cattell (1886) who found that reading colour names required less time than naming colours. Brown (1915), who noticed that this difference persisted after practice, suggested that the two tasks involved separate cognitive mechanisms.

Jensen and Rohwer (1966), in a review of the literature, noted that the accumulated research to date demonstrated:

a) The Stroop procedure was reliable.

b) The timed scores for word, colour and colour-word tasks were of respectively increasing magnitude.

c) The Stroop effect was maintained even after practice.

The form used in the present studies was that of Trenerry et al (1989) consisting of a 'colour' task and a 'colour-word' task.

The Stroop Test and Neurological Studies

Nehemkis and Lewinsohn (1972) were the first examiners to assess Stroop performance with brain-damaged subjects. They found that the colour word task required more time than the colour task for both a normal group and for severely brain-damaged patients. The Stroop procedure was assessed as having considerable potential as a research and clinical tool. Perret (1974) studied patients classified as having frontal, temporal and

posterior brain-damage on a modified Stroop task. Left frontal patients performed significantly more poorly than patients with the other types of lesions. The greatest discrepancy was revealed on colour-word performance. It has been suggested that the left frontal lobe plays an essential role in this form of focused attention (Crawford et al, 1992). Performance of the Stroop test has been analysed using PET (Bench et al, 1993). They found that performance engaged a wide network of anterior brain regions and reciprocal inhibition of posterior brain regions.

Stroop test performance and Schizophrenia

Unmedicated schizophrenic patients have shown impaired visual-motor performance including Stroop and Trail Making at a level two standard deviations below the mean for a control sample (Saykin et al, 1991). Liddle and Morris (1991) found that symotms of incongruity and incoherence were associated with poor performance on the Stroop. Shallice et al (1991) found Stroop colour naming to be particularly poorly performed in their intensive case study of five schizophrenic patients tested on a wide range of putatively frontal tests.

Administration

Administration followed that of Trenerry et al (1989).

Scoring

The subject was timed for each form of the test (maximum 2 mins) and the times and correct responses were recorded. The difference between the number of correct responses for each condition was calculated to give a index of the ability to suppress habitual behaviour in the face of conflicting demands. Normal standardised population data are provided by Trenerry et al (1989).

2.2.3.4 The Continuous Performance Test (CPT)

The Continuous Performance Test is a simple test of sustained attention which requires the S to suppress inappropriate responses. The test was first devised by Rosvold et al (1956). The CPT is used here with schizophrenic patients because symptoms of incoherence of speech and incongruity of affect have been associated with defects in willed action (Frith, 1992). The present studies used a computerised version of the CPT devised by Frith et al (1991).

CPT performance of Neurological and Schizophrenic patients

The CPT has been used with various neurological groups including epileptics and brain injured patients (Greber and Perret, 1985). The CPT has shown both chronic and remitted (drug free) schizophrenic patients to perform poorly on the task (Orzack and Kornetsky, 1966; Wohlberg and Kornetsky, 1973). Frith et al (1991) found that incoherence and incongruity were associated with a failure to inhibit inappropriate

responses on the CPT in their sample of 283 schizophrenics. The present version of the CPT is almost identical to that described by Frith et al (1991) except here 80 stimuli were used instead of 100 (including 20 Es and 20 XEs) as the programme was designed to present stimuli in blocks of 10.

Administration

The S saw a sequence of letters (X,M,T,E) on a VDU at the rate of one every 1.5 seconds. The task required the S to press the space bar on a keyboard every time the letter E appeared, except when it was immediately preceded by the letter X. Eighty letters were presented (10 blocks of 8) including 20 Es requiring a response and 20 Es preceded by an X which do not require a response. All the Ss had two practice sessions of eight trials each to ensure that they understood the demands of the test before the data collection began.

Scoring

Two scores were taken along with mean reaction latencies for each particular type of response: the number of times the S failed to respond to an E (omission error) and the number of times the S responded inappropriately to an E after an X (comission error).

2.2.3.5 The Cognitive Estimation Test

Background

The Cognitive Estimation Test was first conceived by Shallice and Evans (1978). The test was constructed after the authors observed that IQ test scores can be relatively unaffected after substantial frontal damage. Clinical reports of 'frontal' cognitive deficits stress a failure in 'judgement and dealing with novel situations while lower level cognitive skills are retained'; research largely based on the observations of Luria (1966). Shallice and Evans (1978) reported that a patient JS, who showed intact WAIS performance after an explosion, resulting in massive right frontal damage, had a gross inability to produce adequate cognitive estimations. The authors constructed a series of general knowledge questions obscure enough to require answers of one's best estimation. The answers were seen as necessitating the appropriate selection of a suitable cognitive plan and the ability to check any putative answer for 'degree of absurdity' as much as the ability of carrying out the selected plan. An example of a typical question is: 'How heavy is a full pint bottle of milk?'

Description

A modified version of Shallice and Evans (1978) original 26 questions was used in the present studies comprising of 9 questions putatively more sensitive to 'frontal' performance (2,3,4,5,6,9,10,12 and 15) plus the UK population question from the

Information subtest of the WAIS (after Shoqeirat et al, 1990). Normative data on 150 healthy controls have been provided by O'Carroll et al. (1994).

Cognitive Estimation Test performance of Neurological and Schizophrenic patients.

Both alcoholic amnesics and post-encephalitic amnesics demonstrated impairment on the CET (Shoqeirat et al, 1990). Similarly, patients with Korsakoff syndrome have demonstrated significantly impaired CET performance (Taylor and O'Carroll, 1995). These same authors, however, found no significant difference in CET scores between anterior and posterior lesioned patients. Shallice and Evans (1978) found extremely poor CET performance with 4/5 patients in their intensive case study approach to schizophrenia.

2.3 COMPUTERISED NEUROPSYCHOLOGICAL MEASURES FROM THE CAMBRIDGE AUTOMATED NEUROPSYCHOLOGICAL TEST BATTERY (CANTAB)

The CANTAB (Cambridge Automated Neuropsychological Test Battery) is a suite of tasks developed by the Department of Experimental Psychology at Cambridge and the Department of Psychiatry at the Institute of Psychiatry, London (copyright 1991) to measure aspects of visuo-spatial memory, learning, attention and planning in individuals with, or suspected of having, cognitive impairment.

Selected tests were chosen, from the CANTAB, for the present studies with schizophrenic patients according to their theoretical relevance, novel format, accuracy of recording data and ease of use for an often uncooperative set of subjects.

Development of the CANTAB

The measures employed in the CANTAB were developed from animal studies investigating visual discrimination learning and recognition memory. Researchers have found visual discrimination learning, in the form of set shifting behaviour (see later), to be compromised in monkeys with lesions of the frontal cortex (Passingham, 1972). Recognition memory has shown impairment in trained monkeys after selected lesions to the temporal lobes (Mishkin et al, 1982) when a delayed matching to sample paradigm was used. The effects were seen as delay dependent i.e. recognition memory deteriorates more if the delay is increased between sample presentation and choice presentation.

Animals have also been administered computerized visual discrimination problems after training (Roberts et al, 1988). The authors were able to establish that both monkeys and human subjects discriminated between stimuli according to specific attributes of the stimulus rather than relying on discrimination based on reinforcement.

The following computerized tests used in the studies, therefore, comprised specific neuropsychological measures based on previous animal studies for the purpose of highlighting the nature of learning, memory and planning abilities in human populations.

CANTAB provides performance profiles of different patient groups by testing various mental functions across a broad range of abilities (Morris et al. 1987). The presentation medium is advantageous as the tests employ visually attractive non-verbal stimuli and incorporate positive feedback to enhance motivation. The tests require non-verbal responses minimizing the verbal components of the tasks.

In addition, CANTAB contains four parallel batteries which are suitable for repeated testing, especially in investigations involving therapeutic interventions (including drugs) and/or charting the course of illness across time. The use of a touch sensitive screen provided an easy medium for the Ss to respond.

Administration of the CANTAB measures

In the present studies, all CANTAB measures employed an IBM personal computer and a touch sensitive screen (Microvitec Touchtec 501). The S sat approximately .5m away from the screen. Training was carried out using simple psychomotor tests (Motor Screening and Big Circle/ Little Circle-see later) to get the S used to the screen. The S was told to use their dominant hand at much as possible. These initial tests were demonstrated by the E to the S and repeated if the S was unsure of the requirements. This procedure was followed before all CANTAB sessions were attempted.

2.3.1 The Motor Screening Task (from CANTAB)

Description

A series of crosses was shown to the Ss at different locations on the screen. After a demonstration by the Examiner, the Ss were instructed to touch the centre of the crosses as quickly as possible. The test was administered to ensure the Ss could point accurately at target stimuli and to provide an elementary index of the Ss' motor performance.

Instructions and Scoring

Instructions followed the CANTAB manual (?Downes et al., 1991). As this was a preliminary training test, a record of mean response time was the only measure taken to assess any indication of gross motor problems that might confound the utilization of the ensuing tasks.

2.3.2 Big Circle/ Little Circle Test (from CANTAB)

Description

This test was administered as a preliminary training task and to provide an index of the Ss' simple discrimination ability. A series of pairs of circles, one large and one small, was presented to the Ss. They were instructed, initially to point to the smaller of the two as quickly as possible. After 20 trials the Ss were told to point to the larger one.

Instructions and Scoring

The instructions followed the CANTAB manual. The number of correct responses to target stimuli appearing on the left and right hand sides of the screen was recorded along with a total correct score and associated mean reaction times. Again, this task was by way of an introduction to the equipment rather than assessing a particular area of cognitive functioning pertinent to schizophrenia.

2.3.3 EXECUTIVE FUNCTIONING MEASURES FROM CANTAB

2.3.3.1 The ID/ED Set Shifting Task

Set Shifting Ability and frontal pathology

It has been well documented in the clinical literature that patients with frontal lobe pathology exhibit behavioural rigidity or stereotyped behaviour (Luria, 1973). The Wisconsin Card Sorting Test (Berg, 1948; Heaton, 1981) has become an extremely popular tool in clinical neuropsychological studies of frontal lobe pathology. This test of sorting, assessing mental flexibility, appears to be particularly sensitive to frontal lobe pathology, especially when assessing attentional shifting ability (Drewe, 1974; Ciceroni et al, 1983)-see also Introduction p.26. However, the test is not differentially sensitive to frontal lobe pathology and generalised or diffuse brain damage can demonstrate similar cognitive impairment (Robinson et al, 1980). Some studies have shown particular cases where no impairment has been recorded in the face of known frontal lobe damage

(Drewe, 1974). Significant effects have been observed following localized damage to specific non-frontal areas (Canavan et al, 1989). It has also been suggested that such cognitive functions are more vulnerable to the effects of normal aging than other 'non-frontal' functions (Albert and Kaplan, 1980)- more relevantly in performance of the WCST (Haaland et al, 1987). Despite this the WCST has persisted as a major tool in the psychometric investigation of 'frontal-type' behaviour.

Schizophrenia and WCST performance

As schizophrenic patients have been observed as expressing 'frontal-type' behaviours (e.g. psychomotor retardation, behavioural rigidity/perseveration) especially associated with the negative features of the condition (Frith, 1992), the WCST has been widely administered to various groups of schizophrenic patients.

Evidence to support a set shifting impairment (i.e. perseveration in the face of changing contingencies) in schizophrenia has arisen from reports of poor WCST performance in groups of heterogeneous medicated (Morrison-Stewart et al, 1992) and unmedicated schizophrenic patients (Saykin et al, 1991). Recent support for a 'frontal-type' pathology has come from rCBF studies where activation of the dorsolateral prefrontal cortex has been negatively correlated with the number of perseverative errors on the WCST (Weinberger et al, 1988). Such WCST performance is probably not representative of global impairment as groups of 'frontal' patients demonstrated poor results despite having intact WAIS IQs (Milner, 1963). How this can be extended to the performance of schizophrenic patients is debatable, but at least shows that the WCST may tap distinct cognitive impairments characterised by behavioural rigidity, despite other modalities

being intact. However, poor WCST performance has also been recorded in groups of bipolar (manic) patients implying that cognitive inflexibility may be associated with other psychiatric conditions and, therefore, not specific to schizophrenia. Braff et al (1991) proposed that the poor WCST results may be more representative of a sub population of schizophrenic patients of more deteriorated or 'Kraepelian' types. Van der Does and Van den Bosch (1992) noted that not all schizophrenic patients have difficulty with the WCST and those that show an initial impairment performance can actually be improved following brief training.

What does the WCST measure?

Set shifting ability appears to be the main cognitive function of interest in the investigation of mental flexibility or perseveration. However, with the WCST an account of the constituent mechanism of the set-shifting impairment is problematic as the WCST involves several distinct cognitive abilities. Firstly, a matching to sample principle (between two exemplars of a stimulus dimension) is required. In addition, a conditional visuospatial learning ability is necessary to sort out the pack of cards in front of one of four exemplars which remain the same and stay in the same place throughout the test. A S could conceivably show a non-perseverative difficulty in sorting that was due to impaired control over responding by a matching principle or by inappropriate visuospatial associations. A third requirement is to cease responding to a particular dimension and shift to another- again this response probably requires separate cognitive abilities. The WCST involves more than reversal learning and appears analogous to paradigms of intradimensional (ID) and extradimensional (ED) shifts used in human and animal learning experiments (Downes et al.,1989). What we are particularly interested in is using the

ability to shift set whether intra- or extradimensionally as an index of behavioural rigidity in our groups of schizophrenic patients, accounting for both matching to sample and visuospatial learning contingencies simultaneously. The use of complementary subtests from the CANTAB can enable this. The set shifting abilities of the patients can be measured using the Intradimensional/Extradimensional set shifting test while delayed matching to sample and visuospatial abilites can be assessed separately (see later) and compared to the final ID/ED set shifting results.

Explanation of shift behaviour as measured by the ID/ED set shifting test

Animals and humans can attend selectively to a dimension if only one dimension of a compound is reliably correlated with reinforcement. Evidence comes from studies involving compound stimuli, constructed from new exemplars of the original stimulus dimensions, which become the discriminanda for successive stages of learning. If one is required to transfer to such new stimuli, with the dimension relevant to reinforcement remaining constant, one must perform an intradimensional shift (IDS). If the relevant dimension is changed to a previously irrelevant dimension then an extradimensional shift (EDS) is required. Therefore, mental flexibilty can be assessed by the degree to which the S can discriminate the stimuli relevant to reinforcement in the face of different contingencies either along the same dimension or along a previously irrelevant one.

Description of the ID/ED set shifting task from CANTAB (from CANTAB manual, 1991)

In the present studies this computerised test examined the Ss ability to attend to specific attributes of compound stimuli and to shift that attention when required. Two artificial dimensions were used in the test, purple-filled shapes and white lines. Simple stimuli were made up of just one of these dimensions, whereas compound stimuli were made up of both, namely white lines overlying purple-filled shapes (see fig. 1 p. 104).

Ideally, the S progressed through the test by satisfying a set of criterion of learning at each stage (6 consecutive correct responses). If at any stage the S failed to reach this criterion, the test was automatically terminated after a predetermined number of trials (50). The test started with the presentation of two different stimuli along a common dimension, here white lines. The S had to learn which of the stimuli was correct by pointing to it. The computer provided positive or negative feedback for every choice made (stage 1). Once criterion was reached the contingencies were reversed so that the previously incorrect stimulus was now correct (stage 2). The second dimension was then introduced, initially lying adjacent to, and then overlapping, the first dimension. The contingencies did not change, remaining the same at the end of the simple discrimination (stage 3). Once criterion had been reached with the overlapping compound stimulus, the contingencies were reversed within the original dimension (stage 4). It is important to note that the second dimension was entirely redundant to the solution of the problem at this stage.

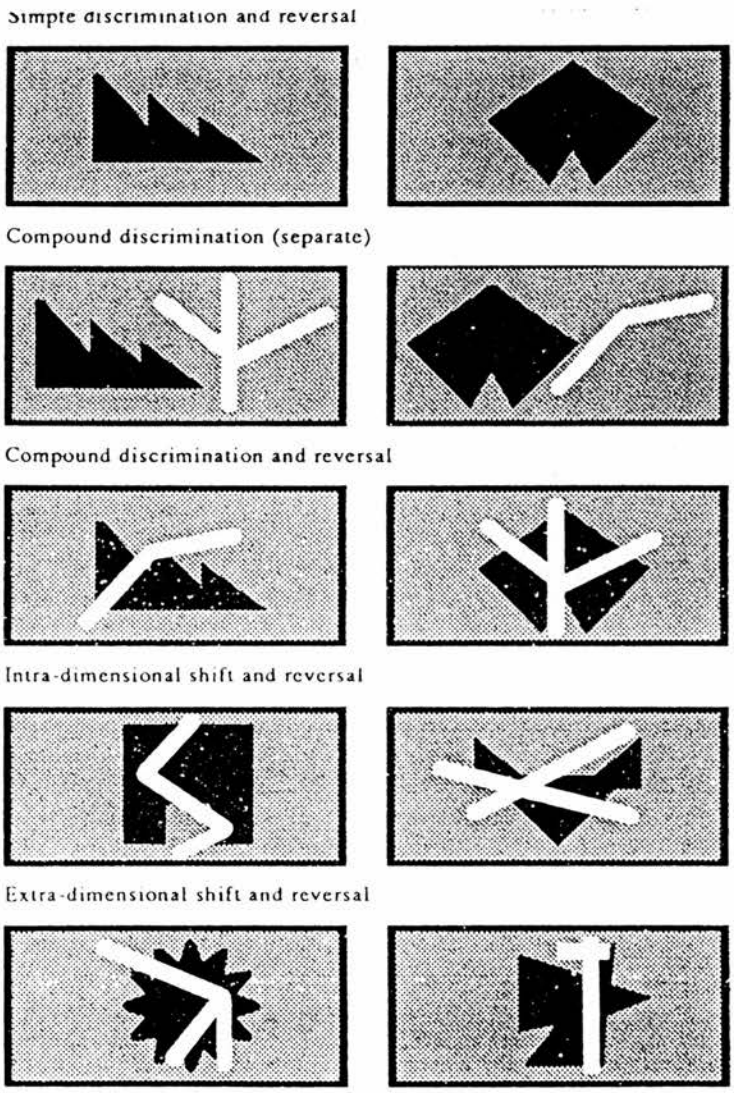

Fig. 1. The nine stages of the ID/ED task.

Once the S had learned the compound discrimination, new compound stimuli were presented, still varying along the same 2 dimensions (of shape and line) (stage 5). The S was then required to continue to attend to the previously relevant dimensions and learn which of the two new exemplars was now correct (this is termed an intradimensional shift) (stage 6). The contingencies were then reversed (stage 7). After this ID shift the Ss were required to shift attention to the previously irrelevant dimension and learn which of the two exemplars in this dimension is now correct (an extradimensional shift) (stage 8) and again, after, the contingencies are reversed depending on success at the first ED stage (stage 9). Nine criteria, therefore, had to be reached for a totally successful performance on the task.

STAGE	DESCRIPTION
1	SIMPLE DISCRIMINATION
2	SD REVERSAL
3	COMPOUND DISCRIMINATION (SEPARATE)
4	COMPOUND DISCRIMINATION
5	CD REVERSAL
6	INTRADIMENSIONAL SHIFT
7	IDS REVERSAL
8	EXTRADIMENSIONAL SHIFT
9	EDS REVERSAL

ID/ED Set Shifting Studies

Roberts et al (1988) found that superiority of ID discrimination learning (over ED) was found for both humans and non-human primates, suggesting common principles governing discrimination learning in both these groups. The most likely interpretation is that both groups were using category information to solve the problem.

Downes et al (1989) compared visual discrimination learning following an ID and ED shift using a 'total change' design in which each shift was made in the presence of novel exemplars of the compound stimuli used as discriminanda with Parkinson's Disease (PD) patients both medicated and unmedicated(early in the course). There was a selective deficit for both groups of PD patients in their ability to perform the ED shift. A similar result was found with medicated, unmedicated, and early in the course (unmedicated) PD patients, interestingly though, these groups were unimpaired on a pattern recognition (i.e. a 'non-frontal') test but were impaired on a computerised planning test which is more associated with problems following frontal lesions (Owen et al, 1992).

Owen et al (1991) assessed attentional set shifting in 20 patients with localised excisions of the frontal lobes, 20 patients with unilateral temporal lobe lesions and 11 patients who had undergone amygdalohippocampus removal. All patients were compared with both young (age-matched) and elderly normal controls on a computerised test of visual discrimination learning involving an IDS and EDS. The frontal lobe patients were selectively impaired in their ability to shift response set to a previously irrelevant dimension but not to a previously relevant dimension-this pattern held for the elderly normal controls. Both the temporal lobe patients and the amygdalohippocampectomy patients were unimpaired in their ability to perform either shift, although both groups had significantly prolonged selection latencies at the EDS stage.

No research appears to have been published, at the time of writing, comparing groups of schizophrenic patients on computerised versions of the ID/ED set shifting paradigm, including comparison of results against symptom expression.

Administration and Instructions (See CANTAB manual)

Scoring

The number of stages successfully reaching criterion were recorded. The number of trials to reach criterion and number of errors incurred on each stage were recorded as an index of visual discrimination learning. The trials to reach criterion on stages 6 (ID shift) and 8 (ED shift) were of particular interest as these 'shifts' were seen as of particular interest as indices sensitive to perseverative responding.

2.3.3.2 A Computerised Version of the Tower of London Test (from CANTAB)

The Tower of London Test (Shallice and McCarthy, 1982) is a graduated problem solving task, involving spatial planning, in which the S must move coloured 'balls' from an initial to a goal position in the smallest number of moves possible.

Background

Shallice and McCarthy (1982) devised the Tower of London test to examine planning ability in groups of patients with frontal lobe lesions. The test was developed after observations of frontal lobe damaged patients who demonstrated a lack of initiative and those organizational abilities necessary for everyday functioning (Luria, 1969). Such impairment has been attributed to those cognitive functions involved in planning (Shallice, 1988). Shallice and McCarthy (1982) found that, in terms of the number of moves taken to complete the task, a group of patients with left anterior frontal lobe damage performed

poorly on the Tower of London task. In comparison, patients with left posterior, and right, anterior or posterior damage did not display impaired performance.

Morris et al. (1988) suggested that in order to solve the Tower of London problems, several cognitive processes are involved. Firstly, a S must generate the sub-units which together comprise the plan, here individual spatial moves. Then, these sub-units must be organized into a sequence which allows them to change the current pattern to the end/goal state. Lastly, the derived sequence must be held in spatial working memory as the solution is being executed.

Description (derived from the CANTAB manual, 1991)

The S was shown two displays of coloured balls (see fig. 2 p. 109). The displays were presented in such a way that they could easily be perceived as stacks of coloured balls held in stockings or socks suspended from a beam. This enabled the S to come to terms with some of the rules of the problems which involve 3-D concepts, and to fit in with the verbal instructions (see later), The S had to use the balls in the lower display to copy the pattern shown in the upper one. The balls could be moved one at a time by touching the required ball, then touching the position to which it should be moved. The time taken to complete the pattern and the number of moves required were taken as measures of the S's planning ability. Initially, it was only necessary to move one ball. The degree of difficulty was then increased in steps to four move solutions. At this point, a procedure controlling for motor performance was inserted. The upper display moved one ball at a time, repeating the moves made by the S in the corresponding previous planning phase. The S had to follow the upper display by moving the balls in the lower display. Again, the

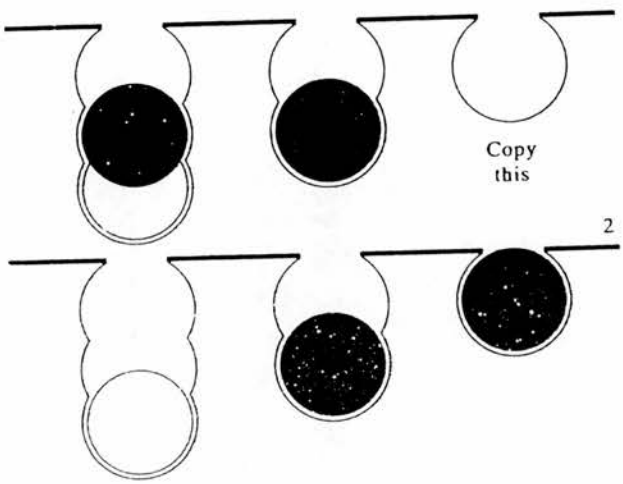

Fig. 2. A two-move problem from the TOL task.

number of moves required increased from 2 to 4. A second block of 2, 4 and 5 moves then followed, and the test was completed by a second block of motor control problems. If the S made more than double the number of moves for the simplest solution, the problem was terminated. If the computer terminated three problems in a row, the whole test was terminated. There was no time limit.

The Tower of London test (CANTAB version) and Neurological studies

Few studies using the new computerised technology have assessed planning ability with patients suffering frontal lobe lesions. However, Owen et al (1990) found that a group of mixed frontal lobe damaged patients required more moves to complete the Tower of London problems than did an age and IQ matched control group. Initial thinking times (experimental-motor control initiation times) did not discriminate between the groups. However, thinking times for moves subsequent to the first move were significantly different, the frontal patients taking longer.

Groups of patients with idiopathic Parkinson's Disease have shown impaired Tower of London performances when medicated (Morris et al, 1988) when number of moves taken to complete the problems and thinking times were analysed compared to matched controls. Owen et al (1992) found that those medicated PD patients with the severest symptoms performed worst on the Tower of London test. Unmedicated PD patients 'early on' in the course of the illness were not impaired on this test. However, both groups were impaired relative to controls on the putative frontal task of set shifting, the ID/ED set shift.

To date there is little published data on the use of the computerised Tower of London with schizophrenic patient samples. The only study known at the time of writing is that conducted by Pantelis et al. (1991) with a group of 45 chronically ill schizophrenic patients. They found that patients exhibiting symptoms of the disorganisation syndrome (see Liddle, 1987a) were significantly slower in their 'thinking' times to initiate problem solving than subsequent thinking time (time to complete the problem after the first move) than patients exhibiting other symptom profiles matched along a range of clinical and demographic variables.

Administration and Instructions (see CANTAB manual)

Scoring

The number of completed sets i.e. trials correctly performed was recorded for each level of task difficulty. Average moves per level of task difficulty were also calculated.

Times to initiate problem solving were calculated for each type of problem. The difference between the time taken to complete each problem and the time taken to complete the yoked following (motor) task per degree of task difficulty was taken as an index of the additional time taken to plan the solution. A 'pure' thinking or 'planning' time was, therefore, calculated for each type of problem. This result was then divided by the total number of moves taken for each solution to yield a 'planning' time per move for each level of task difficulty.

2.4 MEMORY TESTS

Recent research indicates gross memory deficits in groups of schizophrenic patients which are disproportionate to the level of overall intellectual impairment (McKenna et al, 1990; Tamlyn et al., 1992) and disproportionate to deficits on other neuropsychological tests, including putative 'frontal' measures (Saykin et al, 1991).

Mayes and Warburg (1992) suggested that the psychometric assessment of putative memory disorders warrants the selection of a comprehensive battery of tests to provide a profile of a patient's **pattern** of memory impairment.

As stated previously (see Introduction p.35), there is much contemporary evidence to support a fundamental memory impairment in schizophrenia, perhaps underlying at least some of the positive symptoms of the condition, particularly in the formation of delusions (e.g. McKenna, 1991). However, it is also clear that various groups of schizophrenic patients have demonstrated impairments on a range of memory tests putatively measuring different dimensions of memory. It has long been suggested that memory is not a unitary concept. Rather that fundamental aspects of memory include short term (up to 30secs) versus long term storage (for time anything beyond short term) (Baddeley, 1982) and that long term storage has been divided into episodic (memory,usually autobiographical, with a temporal context) and semantic (memory or factual knowledge with no temporal component) memories (Tulving, 1983; Baddeley, 1990). In addition, memory can be further subdivided into visual and verbal components and recognition and recall (i.e. memory with and without external cues, respectively).

The tests that were chosen for the present studies needed to account for the multidimensional nature of memory as a concept. More importantly, the presenting evidence would suggest that an array of memory functions may be impaired in schizophrenia associated with differing symptoms. The tests used, therefore, were intended to fully assess the various aspects of memory previously implicated in schizophrenic neuropsychological dysfunction with different groups of schizophrenic patients. Also, the battery chosen was designed to assess the degree of impairment, if any, against symptom profiles and with regard to performance on other tests putatively measuring different areas of cognition implicated in schizophrenic pathology. The literature justifying the use of each test is relayed alongside the discription of the particular test.

2.4.2 The Rivermead Behavioural Memory Test (RBMT) (Wilson, Cockburn and Baddeley, 1985)

The Rivermead Behavioural Memory Test was constructed to detect impairment in 'everyday' (episodic) memory functioning and to assess change following treatment for memory difficulties (Wilson et al, 1991). The RBMT sought to provide ecologically valid information of memory functioning as opposed to more traditional testing using 'experimental' material. The availability of four parallel forms of the RBMT avoids practice effects associated with repeated testing, a crucial factor in attempting to quantify within subject changes with treatment (see chapter 5).

Reliability and Validity

Standardisation of the RBMT was carried out by administration to 176 brain-damaged patients and to 118 control subjects (Wilson et al, 1989). They found that inter rater reliability and parallel form correlations were highly significant. When RBMT scores were correlated with a battery of tests measuring a wide range of memory functions all results were highly significant, especially recognition memory for words and faces; least significant was performance on a test of sentence verification (Baddeley, 1981) which, although sensitive to brain damage, is less sensitive to everyday memory problems (Sunderland et al, 1983). The RBMT manual (Wilson et al., 1991) provides cut off points for severity of memory dysfunction from an analysis of the relationship between RBMT performance and clinically subjective accounts of everyday memory problems. Additional subgroup cut off points for patients with expressive language problems and those with perceptual problems are also provided (Wilson et al, 1989). These sub group gradations were required because of the mixed aetiologies of brain damage in the original validation group.

The RBMT and Schizophrenia

Several studies have investigated the level of memory functioning, assessed by the RBMT, in groups of heterogeneous schizophrenic patients. Significant impaired performance on the task has been reported disproportionate to the degree of general intellectual impairment and relative to short term memory performance (McKenna et al, 1990; Tamlyn et al, 1992; Duffy and O'Carroll, 1994). This emergent pattern of impairment has been likened to that of the Classic Amnesic Syndrome (CAS) (Baddeley,

1982; McKenna et al, 1990) rather than that found in Alzheimer-type dementia where both short and long term memory functions are affected (Morris and Koppelman, 1986). Duffy and O'Carroll (1994) pointed out that the severity of memory impairment in their schizophrenic patient sample was much milder than that observed in CAS.

When analysing specific tests of episodic memory, Clare et al (1993) found that prose recall and word and face recognition tasks were performed equally poorly when a group of schizophrenic patients were compared with age, sex and estimated pre morbid IQ matched controls. However, Calev et al (1984), found recall deficits to be greater than recognition deficits when using tests matched for degree of difficulty.

Administration

Administration followed that set out in the test manual of Wilson et al. (1985)

Scoring

Aswell as raw scores for the individual tests, a profile score was calculated (0 to 24- 0, 1, 2 per item) which is a sensitive measure of memory function and provides the basis for the categorization of memory dysfunction developed by Wilson et al. (1991).

2.4.3 Digit Span

This is a test for measuring span of immediate verbal recall. As memory has been traditionally divided into short term memory and long term memory (Baddeley, 1982),

the digit span test has been popular in measuring the former e.g WAIS-R (Wechsler, 1981).

Description

The digit span test used in the present studies was taken from the Randt Memory Battery (Randt and Brown, 1983). This was used because there are four parallel versions of the test 'specifically designed for longitudinal studies of patients with mild to moderate impairment of storage and retrieval functions'; the parallel forms are also helpful in looking at drug effects over time (Lezak, 1983).

The Randt digit span test comprised of two tasks; repeating digits forward from 3-9 digits and repeating digits reversed, 2-8 digits in length. Each S was given two chances at each level of task difficulty to correctly recall the digit sequence, failure on both terminated the test. Digit span was defined as the number of items in a string of numbers that a S could immediately recall before termination/end of the test (i.e. maximum forwards = span of 9; backwards span of 8).

Most digit span tests comprise part of a wider investigation of overall cognitive ability e.g. WAIS-R (Wechsler, 1981). However, Tamlyn et al (1992) found that 86% of a heterogeneous group of schizophrenic patients passed a digit span (forwards only) test i.e. scoring 5 on the MEAMS subtest. Duffy and O'Carroll (1994) found no difference on digits forwards and backwards between a group of schizophrenic patients and Korsakoff's patients. Cutting (1985) believed short term memory to be compromised in

schizophrenia, although several contemporary researchers believe STM to remain intact despite poor long term memory (McKenna et al, 1990, Tamlyn et al, 1992).

2.4.4 The Silly Sentences Test (Collins and Quillian, 1969)

Long term memory has been subdivided into episodic (everyday or autobiographical) memory and semantic memory dimensions (Tulving, 1983; Baddeley, 1990). Semantic memory refers to the storage of information without specification for time and place i.e factual knowledge (e.g. What is the capital of France?).

This test was designed to measure the integrity of semantic (factual knowledge) memory through a sentence verification task.

Description

The S was required to classify as true or false 50 statements such as 'Beer is an alcoholic drink' (true) or 'Prime ministers have feathers' (false). The S was encouraged to respond as quickly as possible to each statement.

The Silly Sentences Test and Schizophrenia

Gross deficits in semantic memory performance have been identified, using the Silly Sentences Test. Tamlyn et al (1992) found that their heterogeneous group of schizophrenics performed significantly poorly on the task, aswell as on an episodic memory task, both disproportionately to degree of overall intellectual impairment.

In addition, schizophrenic patients have been seen to perform significantly worse than matched controls on this test (Clare et al, 1993). Duffy and O'Carroll (1994) found an interesting dissociation in their comparison of memory functioning between groups of schizophrenic and Korsakoff's patients. While the schizophrenic patients appeared to have greater episodic memory capability than the Korsakoff's patients, as assessed by the RBMT, their(the schizophrenic patient's) performance on the Silly Sentences Test was significantly worse, both in terms of response time and number of errors.

Scoring

Speed of verification was recorded for each statement as was the number of correct and incorrect responses.

2.4.5 The Auditory Verbal Learning Test (AVLT) (Rey, 1964)

The AVLT is essentially a measure of verbal learning and memory. Specifically, it enables the assessment of immediate memory span, new learning, susceptibility to interference, and recognition memory (Spreen and Strauss, 1991).

Taylor (1959) and Lezak (1983) developed the test for English speaking subjects. The version used in the present studies is that described by Spreen and Strauss (1991 pp. 149-157).

Description

The Ss were required to read a list of 15 nouns (list A) at one second intervals for five consecutive trials. The Ss were required to recall as many words as possible from the list in any order they chose, although the order of the presentation remained constant across all the trials. Instructions for recall were repeated before each trial. After trial 5 of list A another list of 15 nouns (list B) was read to the Ss again for recall just once. After a delay of 30 minutes the Ss were required to recall what they could of the words contained in list A. Finally, the Ss were read a list of 50 words containing all the words from lists A and B and 20 phonemically and/or semantically similar words to those in the two stimulus lists. The Ss were then required to identify solely words from list A. Spreen and Strauss (1991) believe the addition of the recognition stage of the test permits the identification of Ss with retrieval problems who would show better performance on the recognition compared to the recall task.

Studies involving the AVLT.

The AVLT has modest test-retest reliability, over one year intervals (Snow et al, 1988). It has been shown to be sensitive to (left) lateralized brain damage and to verbal memory deficits in a variety of groups (Bigler, 1989; Lezak, 1983).

The AVLT and Schizophrenia

Gray et al (1991) proposed a theoretical model explaining positive schizophrenic symptomatology in terms of a weakening of the influence of memories of previous input on current perception. O'Carroll et al. (1993) used proactive interference as a paradigm to test this hypothesis. The authors tested 3 groups, acutely ill unmedicated schizophrenics, patients with major depressive disorder and healthy controls, on the AVLT. In the event, the resulting PI index, from the AVLT results, did not discriminate between the groups, thus failing to support the Gray et al. (1991) model.

The measure is used in the study of acutely ill schizophrenic patients, here, as an index of new verbal learning and immediate and delayed recall and recognition memory. The AVLT is advantageous in that it allows the assessment of the effect of interference on new learning. Therefore, these dimensions of memory were assessed within the context a larger battery of memory tests and also as a replication of the PI paradigm of O'Carroll (1993) with respect to Gray et al. (1991) model of positive symptomatology. The recording of comprehensive symptom profiles would also allow the assessment of the relationship between specific clusters of symptoms and the dimensions of memory recorded on the AVLT.

Administration and Instructions (see Spreen and Strauss, 1991)

Scoring

The number of correct items was recorded for trials 1 to 5, the post interference trial and for the delay condition. The number of correct items recognized from the 50 item recognition list was also recorded. The difference between the number of correct responses from trials 5 and 6, as a percentage, was also calculated in order to give an indication of the effect of the interference trial (list B) on recall.

2.4.6 Hebbs Recurring Digits Test (see Spreen and Strauss, 1991)

This is an implicit learning test for verbally presented strings of numbers one digit longer than the S's digit forwards span (Milner, 1970). In the present studies, the Ss were unaware that every third string was identical. Normal controls tend to learn this fact quicker than patients with verbal learning difficulties (Lezak, 1983). This test appears to be sensitive to left but not right temporal lobe insults (Milner, 1971). This test appeared in the battery to extend analysis of verbal learning skills and auditory short term memory/attention justified above. Poor Hebb's digits 'time to learn' component has been shown to be significantly correlated with abnormal P300 (an auditory event-related potential) in a group of schizophrenic patients and their relatives compared to normal P300 responders controls (Blackwood et al., 1993).

2.4.7 MEMORY TESTS FROM THE CANTAB

The materials (computer and touch sensitive screen) and preliminary methodology (the setting up of the testing session and the use of introductory tests) for the following CANTAB memory tests were exactly the same as those used for the CANTAB measures described in the tests of executive functioning section.

For all administration/instructions see CANTAB manual (1991).

2.4.7.1 Computerized Short Term Recognition Memory Tests

These computerised tests of short term memory were administered as complementary measures to the more complex CANTAB tests used in the investigation of executive functioning e.g. ID/ED Set Shifting and Tower of London. The recognition tests were used to discriminate the composite neuropsychological elements necessary for the successful performance of the more complex tests. The advantage of using these tests in the investigation of putatively frontal tests is that the former do not appear to be sensitive to excisions of the frontal lobes (Owen et al., 1992).

Computerized Recognition Memory Tests and Neurological Studies

Very few studies using the CANTAB short term recognition tests, described above, have been carried out. Owen et al. (1992) found that both unmedicated and medicated Parkinson's disease patients were unimpaired on pattern recognition despite gross

impairment on a computerized measure of set shifting. Patients with dementia of Alzheimer type (DAT) and medicated Parkinson's disease (PD) patients have demonstrated impairment on both pattern and spatial recognition tests along with deficits on a measure of delayed matching to sample (DMTS) (Sahakian et al, 1988). However, the deficit on the DMTS differentiated the two groups as the DAT patients' deficit was delay dependent and the medicated PD patients deficit was delay independent. To the knowledge of the author at time of writing, no studies involving these type of tests have been used with groups of schizophrenic patients.

2.4.7.2 Pattern Recognition Test

This test of short term pattern recognition memory was derived from animal studies investigating visual memory for lists of objects using a type of serial recognition test (Gaffan, 1974; Mishkin, 1982).

Description

The Ss were presented with series of simple visual patterns for three seconds each in the centre of the screen. The patterns were designed to avoid the possibility of verbal labelling. After a block of twelve patterns had been shown the Ss were instructed to choose between a pattern they had already seen and a novel pattern (different form, same colour). The pairs of patterns in the recognition phase were presented in the reverse order to the original presentation. The Ss were offered feedback for their responses in the way of green ticks and red crosses superimposed on the Ss' responses. The test was then repeated with a new set of twelve patterns.

Scoring

The number of correct responses and the associated mean reaction time was recorded.

2.4.2.3 Spatial Recognition Test

This is a computerized test of short term visuo-spatial memory.

Description

The Ss were shown a white empty square which moved in sequence to five different locations on the screen, each appearing for three seconds each. The Ss were then presented with pairs of squares, one of which was in a location visited by the square in the presentation phase. The other square was situated in an unfamiliar location. As with the pattern recognition phase, the pairs of squares were presented in the reverse of the original presentation order. The test was repeated three more times, each time with five new locations. Again, the Ss were provided with feedback for their responses in the same way as for pattern recognition.

Scoring

The number of correct responses was recorded (maximum=20) along with associated mean reaction latency.

2.4.7.4 Delayed Matching to Sample (DMTS)

The delayed matching to sample measure used in the present studies was similar to that described by Sahakian et al. (1988). Again the use of this test was seen as complementary to the more complex testing. However, successful performance involves the recognition of stimuli along two dimensions, form and colour and the ability to hold information in short term memory across a range of increasingly delayed response intervals. Therefore, performance on this test could be seen as an accurate index of the Ss' non-verbal short term memory abilities in its own right and as an assessment of delay upon the degredation of this memory store. Delayed responding also formed part of the test as patients with frontal lobe damage have shown impairments with testing involving such demands (Petrides, 1985), unlike the non delay dependent pattern and spatial recognition tests.

Description

The test used in the present studies involved both simultaneous and delayed matching to sample. The Ss were shown a complex visual pattern (the sample) that appeared within a red square. The presentation of the sample was preceded by an auditory cue. After a brief delay, four choice patterns were presented under the sample in white squares. Each of these patterns was made up of differently coloured quadrants. Only one of the choice patterns was exactly the same as the sample. One was a distractor pattern, one had the shape of the sample and the colours of the distractor and the fourth had the colours of the sample and the shape of the distractor. One quadrant of all four choice patterns was common with the sample, this was to discourage strategies based on encoding single quadrants. In some trials the sample and the choice patterns were shown simultaneously.

The other trials involved a delay of 0, 4 or 12 seconds between covering of the sample and the showing of the choice patterns. The Ss were given three practice trials with appropriate verbal instructions, and then after 40 counterbalanced trials, including 10 simultaneous and 10 at each of the three delay intervals. If the first choice made was incorrect, the Ss were encouraged to make a second choice and so on until a correct choice was made.

Scoring

The number of correct choices for each of the simultaneous and different delay types was recorded (maximum=10 for each) along with associated mean reaction latencies.

2.5 TESTS OF PSYCHOMOTOR FUNCTION

The following tests were used as indices of psychomotor speed. Recently, Liddle (1987) and Liddle and Barnes (1990) have identified a subsyndrome of schizophrenia characterized by 'psychomotor retardation'; the following tests were administered to give an accurate appraisal of speed of functioning in the studies' groups of schizophrenic patients.

2.5.1 The Digit Symbol Substitution Test

This is essentially a timed test of visuospatial coding from the WAIS-R battery (Wechsler, 1981). It also tests motor persistence, sustained attention, response speed and

visual-motor coordination (Lezak1983). See the WAIS-R manual for administration, instructions and scoring (Wechsler, 1981).

2.5.2 Reaction Time (from CANTAB)

This computerised test of reaction time formed a part of the larger procedure of tests administered from the CANTAB. The preliminary methodology described in the executive functioning section was again followed so that the Ss were used to the demands of responding to a touch sensitive screen which the present test required.

Description

The task was divided into five consecutive stages involving increasingly more complex responses. The Ss were instructed to respond with their dominant hand at all times, placed on the desk .5m from the touch sensitive screeen, if possible. Firstly, the Ss had to touch the screen, as quickly as possible, when a small yellow dot appeared in the centre of a larger empty white circle. Responding too soon or too late to the dot resulted in a void trial. Once the Ss had scored 5/6 correct responses or completed a maximum of 18 attempts, a choice reaction task was introduced. The yellow dot now appeared in one of five locations; the Ss must again achieve 5/6 correct responses in a maximum of 30 attempts. If the Ss failed to reach criterion in the first two stages the test was terminated. On successful completion of the second stage the Ss were introduced to a manually operated pad that they were instructed to hold down until the yellow dot appeared in the centre of the screen. The Ss at this stage did not have to touch the screen. In the fourth stage the Ss were again instructed to hold the pad down until the yellow dot appeared

and then, with the same hand, were told to touch where the dot appeared. The fifth and final stage was a choice reaction task base on the procedure at stage four but involving five possible locations where the dot could appear. At this stage the Ss had to reach a criterion of 5/6 correct responses within a maximum of 40 attempts.

The task parameters consisted of a stimulus display time of 250 msecs, hold on the pad was limited to 5000 msecs and each intertrial interval was 1000 msecs.

Scoring

Simple reaction times were recorded for stages 1 to 3. Stages 4 and 5 involved a reaction latency and a movement latency. The movement latency was calculated as the time from the dot appearing (after the pad had been pressed) and the Ss releasing the pad. The reaction latency was calculated as the time between releasing the pad and touching the screen. A subtraction of the motor times from the reaction latencies, therefore, resulted in a pure 'thinking' time index independent of motor problems.

2.6 TESTS OF VISUOSPATIAL NEGLECT

A wealth of neuropathological, neuropsychological and neuroimaging studies have demonstrated asymmetries in brain functioning in various groups of schizophrenic patients (see Introduction p.40 and below). However, researchers are divided whether dysfunction can be attributed to the left (Crow, 1990; Friston et al., 1992) or to the right (Cutting, 1985) cerebral hemisphere. For the present studies, cancellation tests involving verbal and non-verbal stimuli and a line bisection estimation test, after Wilson et al.

(1987), were used to assess the degree of hemispatial neglect expressed by the different groups of schizophrenic patients.

Visuospatial Asymmetry and Schizophrenia

Studies of 'circling behaviour' in schizophrenia have indicated right hemispatial neglect as characterizing the behavioural asymmetry in this groups of patients (Bracha, 1987; Lyon and Satz, 1991). Tomer and Flor-Henry (1989), however, found that, using simple cancellation, tests there was a relative shift in hemispatial neglect from right to left when patients scores were compared when in an unmedicated state and after a period on medication. This relative shift in hemispatial neglect was not replicated by O'Carroll et al. (1995) who found that although a group of chronic schizophrenic patients demonstrated significantly more omissions than unmedicated schizophrenic patients, patients with major depression and healthy controls, there was no difference in omission asymmetry scores between the groups. Mather et al. (1990) in an analysis of asymmetry found no difference in performance between schizophrenic patients and controls using the line bisection task. So, although groups with specific hemispheric insults using the line bisection task appear to show a hemispheric asymmetry in function (Heilman and Valenstein, 1978), this effect may be more subtle in schizophrenia. The lateralization effects seen may be of higher order functioning not sensitive to crude tests of hemispatial neglect, such as line bisection (Mather et al., 1990). The line bisection test was used in the present studies to complement the other tests of neglect and to see whether a functional lateralization effect may be characteristic of particularly defined groups of schizophrenic patients or may be associated with the expression of particular symptoms, or may change in concert with symptomatic improvement.

Description

Cancellation Tests (from Wilson et al. (1987) Behavioural Inattention Test)

A test of letter cancellation was used. This comprised of a sheet of paper containing 4 rows of 34 letters. The Ss were instructed to cross out all the 'Es' and 'Rs' on the page, in their own time. A star cancellation test was then administered. This test consisted of a sheet of paper containing large and small stars, letters and short words randomly arranged. The Ss were this time told to cross out all the small stars they could see, again in their own time.

Line Bisection Test

The Ss were presented with a sheet of paper on which were three staggered lines each 204 mm in length. The Ss had to estimate the midpoint of each line and mark it with a cross.

Scoring

For both of the cancellation tests the number of omissions for each hemispace were recorded. Following Tomer and Flor-Henry (1989) an asymmetry index was calculated by subtracting the number of right hemispace omissions from the left hemispace omissions, the result was then divided by the total number of omissions. Therefore, a positive value indicated a neglect in the right hemispace and vice versa.

An asymmetry index was also calculated from the line bisection performances. The length of each line right of the estimated midpoint was subtracted from the length to the left. The three lengths in mm were then added and divided by three to give an average asymmetry index. Again, a positive value was indicative of right hemispatial neglect and vice versa.

2.7 The Positive and Negative Syndrome Scale (PANSS) (Kay et al. (1989)

The psychiatric rating scale used in chapters 3-5 was the Positive and Negative Syndrome Scale (PANSS; Kay et al. (1989)-see appendix 3). This scale was developed and constructed along the guidelines for test construction laid out by the American Psychological Association (1985). The result was a thrity point item scale including seven positive symptoms and seven negative symptoms of schizophrenia. In the present studies only the particular symptoms directly relevant to schizophrenia were used in analysis, the remaining sixteen symptom ratings refer to general states of psychopathology e.g anxiety. The positive items, used in the present studies, included delusions, conceptual disorganisation, hallucinatory behaviour, excitement, grandiosity, suspiciousness/ persecution and hostility. The negative or deficit symptoms included blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking. Although such symptoms as stereotyped thinking have been considered as not exactly positive or negative as traditionally understood (Frith, 1992), the items included in the scale, as a whole, were picked to be broadly representative of symptoms from the cognitive, social, emotional and communicational realms of clinical pathology expressed

by schizophrenic patients (Kay, 1990). The authors also held that such a scale was generally more sensitive to other established scales e.g. BPRS (Overall and Gorham, 1962) in terms of the types and degree of symptom expression able to be recorded (Kay et al., 1989). The PANSS is, therefore, sensitive to a wide range of schizophrenic symptomatology and, is also sensitive to the severity of symptoms, by including a seven point scale of severity from absent through minimal, mild, moderate, moderately severe, severe and extreme expressions of the symptom. Studies have shown a high degree of inter rater reliability and validity with other scales e.g. Andreasen and Olsen (1982) scale (Kay et al. 1988, 1989b). With the scale comes formal criteria for conducting the psychiatric interview and a video training package. The PANSS was used, in the present thesis in chapters three to five, as a comprehensive analysis of presenting symptom states, especially useful for the empirical analysis of symptom ratings that formed the basis of chapters three and four.

CHAPTER 3: NEUROPSYCHOLOGY AND SYMPTOMS OF CHRONIC SCHIZOPHRENIA

3.1 INTRODUCTION

Any investigation of the putative underlying cognitive deficits associated with schizophrenic behaviour is problematic due to the hetrogeneous nature of the behaviours expressed by those patients diagnosed as schizophrenic. This problem has encouraged researchers to find new ways of categorising the behaviour of schizophrenic patients. Researchers hoped, therefore, that clinical, physiological or neuropsychological information, may be understood more clearly in context with variables such as related behaviours or symptom clusters, chronicity of illness or treatment response.

The traditional dichotomy of positive (abnormal experiences) and negative (absence of normal functioning) symptoms arose from the respective types of symptoms having little correlation with each other (Mortimer et al., 1990). Studies have shown distinct cognitive profiles associated with positive and negative symptoms respectively (e.g. Nelson et al., 1990; Addington et al., 1991), usually with negative symptoms associated with greater cognitive slowing. The positive-negative dichotomy led Crow (1980) to suggest that two differing sub pathologies of schizophrenia might exist, one associated with positive symptoms and good treatment response to dopamine antagonists (type 1) , the other characterised by a deficit state, poor treatment response and cortical atrophy resulting in poor cognitive functioning (type 2). Although

Crow's classification allowed patients to express both types of symptoms simultaneously, some central symptoms, associated with schizophrenia, have been suggested as falling into neither 'pathological camp' i.e. stereotyped behaviour (Frith, 1992).

In order to clarify the relationship between symptoms, Liddle (1987) and Liddle and Barnes (1990), rated chronically ill, but stable, schizophrenic patients on the Comprehensive Assessment of Symptoms and History (CASH; Andreasen, 1983) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982) and the Manchester scale (Krawiecka et al., 1977) in the respective studies. This approach was based entirely on associations between presenting signs/symptoms and not on idiosyncratic theoretical models of the condition. Using factor analysis of the emergent ratings the investigators were able, empirically, to produce three clusters or syndromes of related symptoms. The syndromes generated were coined 'psychomotor poverty' (including: poverty of speech, flattened affect and decreased spontaneous movement), disorganisation' (incoherence of speech and inappropriate affect) and 'reality distortion' (hallucinations and delusions). The authors hoped that these emergent syndromes represented different underlying sub pathologies of illness with distinct cognitive profiles. Subsequent work, on the cognitive dysfunction that might underlie these syndromes, revealed significant associations between psychomotor poverty and slowness of mental activity, in particular word generation. Disorganisation was significantly associated with poor performance in suppressing inappropriate responses. Reality distortion was only related to impairment in figure-ground perception (Liddle, 1987) but not significantly

related to cognitive testing on a range of purtative 'frontal' tests (Liddle and Morris, 1991). The first two syndromes were proposed as different expressions of frontal lobe dysfunction, while reality distortion was putatively related to an abnormality of the temporal lobes. Such conclusions have been partially supported by PET studies (Liddle et al., 1992), although the authors admitted that the rCBF results indicated that the brain abnormalities associated with each syndrome would involve wider more distributed neural networks than the foci indicated previously from the neuropsychological studies.

Other studies have replicated Liddle's empirical studies (Johnstone et al., 1991; Brown and White, 1992). However, Brown and White (1992) did not find any neuropsychological sequelae associated with disorganisation and suggest that psychomotor poverty may result from expressions of extrapyramidal side effects.

Liddle's factor analysis approach is, of course, dependent on the content of the scales used for analysis. Some researchers have called into question the use of factor analytic measures, as clusters of related symptoms are bound to appear whatever the data set to which they are applied (Kendall, 1975). This would call into question the meaningfulness of any emergent clusters. In addition, inflation of the correlations between symptoms may result from the use of solely hospitalised samples (Bentall et al.,1988). It would appear to be important, therefore, that such studies use valid rating scales particularly designed to cover the widest range and degree of schizophrenic symptoms derived from clinical experience and operational criteria. Also, differing groups characterised by status and chronicity ought to be involved to check the reliability of the Liddle

subpathologies across different populations of schizophrenic patients (see also Neuropsychology, Symptoms and Acute Schizophrenia chapter).

3.1.1 Purpose of the Study

The purpose of the present study was to address some of the issues cited above to develop the methodology of Liddle and colleagues in a more exhaustive understanding of the inter-relationship between schizophrenic symptoms and the cognitive characteristics of any meaningful empirically derived sub syndromes of illness. An opportunity to explore this was offered by the recruitment of an extremely large group of schizophrenic patients (over twice the number ever used in the Liddle et al., samples) of chronic status, who represented a wide range of long term hospital based patients and those who had been community based for some time.

3.1.2 Aims of the Study

The purpose of the present study was to replicate Liddle's syndromic approach to the signs and symptoms of schizophrenia. The object of the study, specifically, was to clarify if the proposed syndromes of chronic schizophrenia can be shown to exist in a large sample of patients using a new more comprehensive rating system; the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989) than more traditional and limited, rating scales used to date, in terms of type and severity of symptoms.

Again, with regard to contemporary research and theoretical modelling of schizophrenic symptoms, the neuropsychological investigations of syndrome expression to date have been limited, by the type and range of neuropsychological measures used. The present study's intent was to use a larger battery of contemporarily relevant neuropsychological measures to assess syndromic associations with functioning considered as underpinning a wide range of schizophrenic symptoms. Relevant measures were grouped under executive or 'frontal', memory, psychomotor and hemispatial functioning domains. As explained more thoroughly in the Methods chapter, these particular domains of functioning appear to be characteristic of the major areas of cognitive dysfunction observed in various heterogeneous groups of schizophrenic patients. The methodology of investigating the association between cognitive dysfunction and symptom expression has been less well documented, but none the less important. The use of this methodology, in research into the neuropsychology of schizophrenia, has been gaining ground and has lead to a more definitive understanding of the cognitive mechanisms that underpin the various expressions of schizophrenic behaviour (Corcoran and Frith, 1993).

Executive or 'frontal' problems have been widely observed in schizophrenic patient samples (Kolb and Wishaw, 1983; Shallice et al., 1991) and have been associated with a fundamental deficiency in the Supervisory Attention System (SAS) in the control of self generated activity. Support for this has come from the the inability of schizophrenic patients, displaying first rank symptoms, to monitor their own self generated actions (Frith and Done, 1989). Symptoms

derived from this impairment migh include third person hallucinations and passivity phenomena. With the previous Liddle et al., studies in mind, it was deemed necessary to include tests both of executive type and psychomotor measures to assess both inappropriate responding (related to incoherence and incongruity of affect) and cognitve speed (related to deficit state symptoms). Memory measures were deemed as extremely important as, not only have specific disproportionate memory deficits been observed in heterogeneous groups of schizophrenic patients (McKenna et al., 1990; Tamlyn et al., 1992; Saykin et al., 1991) but memory impairments have been associated with delusions, hallucinations and thought disorder, in terms of the generation and use of 'false knowledge' in contemporary functioning (Mortimer and McKenna, 1994). Episodic memory dysfunction has also been suggested as underpinning symptoms such as paranoid delusions and poverty of social and communicative functioning (Frith, 1992). These symptoms might result from poor social judgements due to either a misinterpretation of others actions (due to faulty social cogntion) or a poverty of accessible social knowledge for successful interaction. This battery of tests should, therefore, be able to establish the underlying cognitive dysfunction, if any, associated with any emergent syndrome. A closer investigation of the effect extrapyramidal side effects was warranted as syndromes such as psychomotor poverty may be allied to treatment effects. The neuropsychological performance of the patients necessitated being put into context with normal functioning and thus a comparison with healthy controls was carried out.

The design of the study allowed a comprehensive analysis of the relationship between the symptoms expressed by a large, and varied, group of chronic schizophrenic patients and how any emergent groups of related symptoms were associated with comprehensive neuropsychological performance. In addition, there was the opportunity to compare neuropsychological functioning with a group of healthy controls allowing an appreciation of the degree and nature, if any, of cognitive impairment, displayed by the schizophrenic patient group.

3.2 METHOD

3.2.1 Subjects

Sixty six patients with DSM-IIIR (American Psychiatric Association, 1987) diagnoses of chronic schizophrenia were recruited. The patients were either in- or out-patients of the Royal Edinburgh Hospital. Forty patients were recriuted from the RIS-GBR-006 study of treatment resistant schizophenia, see chapter 5 for the definition and selection of these patients. The other twenty six patients were independently recruited by the investigator from the REH. Twenty five controls (13 males, 12 females) were also tested on the neuropsychological measures. All patients and controls were screened for alcohol and/or drug abuse, history of head injury, and for the patients, history of ECT in the previous six months. None of the controls had any history of psychiatric problems whatsoever. Age, sex and number of full time years of education are recorded on table 6 for both groups. Hospitalisations, duration of illness and drug histories to be added can also be see on table 6.

3.2.2 Psychiatric Ratings

All patients were assessed on the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1989) to cover a wide range of positive and negative symptom ratings. Full details are given in the main Methods chapter. The patients were also assessed on the Abnormal Involuntary Movement Scale (AIMS; US Department of Health, Education and Welfare, 1976) and the Targeting Abnormal Kinetic Effects (TAKE) scale (Wojcik et al., 1980) for evidence of extra pyramidal side effects at interview. All psychiatric ratings and movement disorder scales were carried out by experienced and trained psychiatrists.

3.2.3 Neuropsychological Measures

As stated above, the chronically ill patients and the control group were tested on a battery of neuropsychological tests designed to measure/target the cognitive deficits that may underlie those symptoms that characterise a group of relatively stable chronically ill patients with a diagnosis of schizophrenia. The measures used are discussed fully in the main Methods chapter.

General intellectual functioning was measured by using the National Adult Reading Test (NART) (Nelson, 1982) as an index of pre morbid ability. Current intellectual ability was measured with the Quick Test (Ammons and Ammons, 1962).

Executive functioning was measured by using a verbal fluency task (initial letter 'A' and Animal categories) (Spreen and Strauss, 1991), a computerised Continuous Performance Test (CPT) (Frith et al, 1991), the Stroop test (Trenerry et al., 1989) and the Trail Making Task (A&B) (Reitan, 1958). Two further computerised tests of executive functioning were administered from the CANTAB (Robbins et al., 1991); the Intra/Extradimensional Set Shifting task and the Tower of London task- a measure of planning ability.

Memory functioning was assessed by the Rivermead Behavioural Memory Test (RBMT) (Wilson et al., 1985), a measure of long term episodic memory, and digit span forwards and backwards to assess short term verbal working memory (Randt and Brown, 1983) . A computerised Delayed Matching to Sample task was also administered from the CANTAB (Robbins et al., 1991) to assess delay dependent non verbal short term memory. Measures of pattern and spatial recognition memory were also administered from the CANTAB practice battery.

Psychomotor functioning was assessed using the reaction and motor time measure from the CANTAB (stage 5 of the Reaction Time measure) and the Digit Symbol Substitution Test (from the WAIS-R, Wechsler, 1981).

Tests of **hemispatial neglect** were also administered to assess hemispatial acuity. Letter and star cancellation tests and a line bisection task (Wilson et al., 1987) were used.

Details of the administration and scoring of all the above tests with theoretical backgrounds can be seen in the main Methods chapter.

All subjects were tested at one sitting, if possible, if not, all were done on the same day with convenient breaks. The patients' performance from the RIS-GBR-006 was recorded from baseline. The psychiatric ratings and movement disorder scales were carried out on the same day as testing (+/-1).

3.2.4 Data Analysis

Factor analysis was undertaken with rating scores of the 14 signs/symptoms (7 positive, 7 negative) from the PANSS scale (see appendices for scale). Analysis was similar to that carried out by Liddle and Barnes (1990). Initial factors were extracted by the method of principal components. An oblique rotation was performed as, prior to Liddle (1987) and Liddle and Barnes (1990), there was no a priori evidence that symptoms should be related. Factor scores were calculated by the regression method. All analyses were performed using SPSS 4.0 on a Macintosh personal computer.

Pearsons correlations (two-tailed) were carried out between factor scores and neuropsychological test results of the chronically ill schizophrenic patient group. Partial correlations were also obtained for this relationship after correcting for extrapyramidal side effect ratings due to Brown et al. (1991) having shown that tardive dyskinesia itself to be associated with 'frontal' type psychological

deficits. Partial correlations were also obtained, correcting for Quick IQ i.e. current IQ, as current IQ was seen as significantly associated with the third significant emergent factor in preliminary analysis. Therefore, it was deemed necessary to statistically account for the effect of current IQ performance on the relationship between syndrome 3 score and the more specifc neuropsychological test performances.

The chronic schizophrenic patients results were compared with the control group to assess the degree of any domain specific dysfunction. Test performance between the two groups was analysed by combining the measures into groups by function i.e. executive function performance, memory performance etc. Comparison was calculated using the multivariate analysis of variance (MANOVA) to assess any overall effects by function. In the case of test results expecting missing data due to the design of the test i.e. fewer subjects reaching the more difficult stages of the ID/ED Set Shifting Task, chi squared statistics were used to analyse the proportion of subjects per group reaching each stage of the Set Shifting Task. The between group comparison was also repeated using full time years of education as a covariate as preliminary analysis revealed superior educational experience in favour of the control group.

3.3 RESULTS

3.3.1 Factor analysis

Factor analysis generated four groups of related symptoms (see table 1). Only those factors yielding an eigen values greater than one were considered statistically meanigful for further analysis. The first factor or 'syndrome' loaded heavily on delusions, hallucinations and suspiciousness/ persecution. This factor accounted for 23.4% of the variance in scores. The second factor was characterised by lack of spontaneity and flow of speech, poor rapport, emotional withdrawal and passive/apathetic social withdrawal. This factor accounted for 18.4% of the total variance of scores. The third factor revealed association in ratings between difficulty in abstract thinking, conceptual disorganisation, and stereotyped thinking, accounting for 14.9% of the total variance in scores. The fourth and last factor showed related ratings between grandiosity and hostility, accounting for 8.4% of the total variance in psychiatric scores. Almost 35% of the variance of scores, therefore was not accounted for by the emergent factors.

3.3.2 Correlations between neuropsychological test performance and factors/syndromes (see table 2 for individual correlations)

Syndrome 1, characterised by hallucinations and delusions, did not correlate significantly with performance on any of the neuropsychological tests.

Syndrome 2, characterised by poverty of sociability and affect, showed significant positive correlations with verbal fluency-semantic category, digit span forwards and Rivermead Behavioural Memory Test (RBMT) profile scores.

Syndrome 3, encompassing conceptual disorganisation and difficulty in abstract thinking, was highly negatively correlated with current IQ (Quick IQ), digit span forwards and backwards and Rivermead Behavioural Memory Test profile scores. Verbal fluency (words beginning with letter 'A'), Continuous Performance Test (CPT) total target letters ('E's) and inappropriate responses (positive correlation), pattern and spatial recognition memory test results were less highly but still significantly correlated with syndrome 3.

Syndrome 4, characterised by grandiosity and hostility, was not significantly correlated with any neuropsychological test performance.

Correlations between Tower of London Test results and syndrome scores can be seen on table 3.

Syndrome 1 was significantly negatively correlated with motor initiation times for four move solutions and significantly positively correlated with initial 'planning' times for two move solutions.

Syndrome 2 was significantly negatively correlated with initial 'planning' time for four move solutions only.

Syndrome 3 was significantly negatively correlated with the number of completed sets for all (two to five move solutions) levels of task difficulty.

No performance variables from the Tower of London Test were significantly correlated with syndrome 4 scores.

As syndrome 3 was highly correlated with current IQ, the correlations were repeated to produce partial correlations after correcting for Quick IQ scores. This procedure was carried out to allow for the influence of current global IQ scores on the other more specific neuropsychological test performances. The analysis revealed digit span forwards ($r=-.3058$, $p<.05$) and backwards ($r=-.2519$, $p<.05$), and RBMT profile scores ($r=-.2409$, $p<.05$) to be still significantly, negatively, correlated with the syndrome but at a reduced level of significance. CPT total number of target letters correct was significantly negatively correlated at the same level of significance ($r=-.3058$, $p<.05$). The verbal fluency, pattern and spatial recognition memory tests and the CPT inappropriate responses correlations all became non significant.

As far as the Tower of London results were concerned, no significant correlations were produced in terms of number of completed sets. This procedure did, however, expose significant negative correlations for motor initiation times for two move solutions ($r=-.2500$, $p<.05$) and 'planning times' per move subsequent to the first move for three move solutions ($r=-.2501$, $p<.05$).

3.3.3 Neuropsychological test performance, syndrome scores and extra pyramidal side effects (see tables 4&5)

Partial correlations, of syndrome scores and neuropsychological test performances, were calculated, correcting for extrapyramidal side effect ratings (AIMS & TAKE), as researchers have found that such common side effects as tardive dyskinesia to be related to 'frontal' or executive type deficts on psychological testing (see Brown et al., 1991).

After this procedure:

Syndrome 1 was not significantly correlated with any test performance.

Correcting for TAKE scores, the verbal fluency 'animals' scores, CPT inappropriate responses and digit span forwards were all highly positively partially correlated with syndrome 2. To a lesser, but still significant, level of significance, Quick IQ scores, verbal fluency initial letter 'A' scores, CPT number of target 'Es', spatial recognition memory test scores, digit span backwards, RBMT profile scores were significantly positively partially correlated with syndrome 2 scores; motor latency stage 5 from the CANTAB reaction time measure was significantly negatively partially correlated with syndrome 2. Correcting for AIMS scores, high positive significant partial correlations were revealed between verbal fluency initial letter 'A' and semantic category 'Animals' and digit span forwards with syndrome 2.

As far as partial correlations with syndrome 3 were concerned, after correcting for TAKE scores, highly significant correlations were revealed between the syndrome and Quick IQ scores, CPT inappropriate responses (positively), digit span forwards and backwards and RBMT profile scores (all negatively unless otherwise stated). Verbal fluency initial letter 'A', CPT number of target 'Es', Stroop word-colour scores and pattern recognition memory performance also produced significant partial correlations with syndrome 3, but at a lower level of significance. The same significant correlations were generated after correcting for AIMS scores.

Number of completed stages of the ID/ED set shifting task, trail making task (B-A) times and letter asymmetry indices were significantly partially correlated with syndrome 4 when correcting for TAKE scores. Only trail making and letter asymmetry indices were significantly partially correlated with syndrome 4 when correcting for AIMS scores.

As far as the Tower of London performances were concerned, partial correlations, with correcting for TAKE scores, revealed significant correlations between syndrome 1 and motor initiation and subsequent motor times for four move solutions (both negative), and initial planning times for two move solutions (positive).

Syndrome 2 was significantly negatively partially correlated with subsequent planning times per move for three move solutions.

Syndrome 3 was significantly positively partially correlated with average moves for four move solutions and times per move subsequent to the first move for five move solutions.

No Tower of London variables were correlated significantly with syndrome 4 after correcting for TAKE scores.

Correcting for AIMS scores, revealed negative significant partial correlations with syndrome 1 for motor initiation times for three and four move solutions, a high significant correlation with subsequent (to the first move) motor times for four move solutions. Initial planning times for two move solutions were significantly positively correlated with syndrome 1.

After correcting for AIMS scores, initial planning times for four move solutions and planning times per move subsequent to the first move for three move solutions were significantly negatively partially correlated with syndrome 2.

In the same vein, syndrome 3 revealed only one significant negative partial correlation with planning times per move subsequent to the first move for five move solutions.

No significant partial correlations were recorded between neuropsychological test performances and syndrome 4.

3.3.4 Neuropsychological test performance of Chronic Schizophrenic patient group versus Controls

3.3.4.1 Demographics and General Intellectual functioning (see table 6)

The groups were well matched for sex ratio, age and pre morbid IQ (assessed by NART error scores) and current IQ (Quick IQ performance). However, the controls demonstrated significantly greater educational experience, in terms of the number of full time years of education, than the chronic schizophrenic patient group.

The between analysis of neuropsychological functioning was, therefore, carried out with and without the number of full time years of education as a covariate. This was to assess the effect of the disparity in education background on the comparison of neuropsychological performance as education appears to have a 'potent and pervasive' influence on nearly all types of neuropsychological test performance (Lezak, 1983).

3.3.4.2 Executive functioning performance (see table 7)

An extremely high significant difference was observed, showing better performances on an array of executive functioning tests in favour of the control group. Univariate analyses showed the chronic patient group to be functioning at extremely lower levels of executive functioning as assessed by verbal fluency (both initial letter and semantic categories), number of completed stages and

trials to reach stage six (an intradimensional shift) on the ID/ED set shifting task, numbers of correct and inappropriate responses recorded from the Continuous Performance Test (CPT), Stroop word- colour condition results and trail making part B-A times. A trend towards significance was observed on trials to reach stage eight (an extradimensional shift) on the ID/ED set shifting task.

After controlling for education background, the highly significant overall difference in executive functioning remained. As far as univariate differences were concerned, CPT correct response performance was the only performance variable that changed to non significance. Trials to criterion on stage eight of the ID/ED set shifting task now showed no trend toward significance.

Table 8 shows the proportion of subjects passing each stage of the ID/ED set shifting task. Apart from simple discrimination and simple reverse discrimination, stages one and two, all other stages showed a higher proportion of controls passing those stages i.e. reaching criterion than the chronic schizophrenic patients, including stage six (an intradimensional shift) and stage eight (an extradimensional shift).

Analysis of the Tower of London test results for the groups can be seen on tables 9 to 14. No overall difference in number of completed sets was observed, though univariate analysis showed significantly fewer five move problems completed by the patients. This, however, became non significant after controlling for education. A significant overall difference in number of average moves to complete each type of problem was seen in favour of the controls,

particularly concerning three and five move problems. This difference was still significant after controlling for education but at a lower level of significance.

The controls showed overall quicker motor times to initiate problem solving especially for three, four and five move problems. The overall difference became non significant after controlling for education. There remained significant univariate differences for three and five move problems despite this. Motor times subsequent to the first move also showed large differences with the controls being far quicker completing two, three and four move problems. These differences remained, still at high level of significance, after controlling for education.

No overall differences were seen between the groups when planning times per move to initiate and complete the Tower of London problems were analysed. Despite this, after univariate analysis, only planning times for five move problems, subsequent to the first move, were significantly different before and after controlling for education in favour of the controls.

3.3.4.3 Memory test performance (see table 15)

An extremely high overall level of significance was recorded both before and after controlling for education on an array of memory tests. The control group appeared to be vastly superior on many measures of memory functioning compared to the patient sample, in particular delayed matching to sample, pattern and spatial recognition memory, digit span backwards and Rivermead

Behavioural Memory Test (RBMT) profile scores. No significant difference was seen on digit span forwards performance. The difference in simultaneous matching to sample became non significant, after controlling for education.

3.3.4.4 Psychomotor ability (see table 16)

The control group were vastly superior on tests measuring psychomotor performance,

this was unaffected by controlling for education.

3.3.4.5 Hemispatial neglect and lateralisation (see table 17)

No overall or univariate differences were revealed after comparing the groups' hemispatial acuity on tests of hemispatial neglect.

TABLE 1

FACTOR LOADINGS OBTAINED BY FACTOR ANALYSIS OF SYMPTOMS

SYMPTOMS	FACTOR 1	FACTOR 2	FACTOR 3	FACTOR 4
DELUSIONS	.797	-.027	.006	-.256
HALLUCINATIONS	.776	.142	.121	.159
SUSPICIOUSNESS/ PERSECUTION	.773	-.187	-.084	-.280
BLUNTED AFFECT	.495	-.035	-.067	.438
PASSIVE/ APATHETIC SOCIAL WITHDRAWAL	.271	-.722	-.076	.148
HOSTILITY	.267	-.096	.051	-.684
EMOTIONAL WITHDRAWAL	.250	-.779	-.149	-.132
STEREOTYPED THINKING	.230	-.239	.526	-.216
EXCITEMENT	.140	.452	.458	-.238
CONCEPTUAL DISORGANISATION	.008	.061	.816	-.130
GRANDIOSITY	-.049	.070	.028	-.746
DIFFICULTY IN ABSTRACT THINKING	-.053	.073	.827	.199
POOR RAPPORT	-.208	-.800	.122	-.248
LACK OF SPONTANEITY AND FLOW OF SPEECH	-.212	-.825	.303	.215
EIGEN VALUE	3.272	2.574	2.087	1.181
% VARIANCE	23.4	18.4	14.9	8.4
CUM % VARIANCE	23.4	41.8	56.7	65.1

TABLE 2

CORRELATIONS OF SYNDROME SCORES AGAINST NEUROPSYCHOLOGICAL TEST PERFORMANCE

TEST	SYND1	SYND2	SYND3	SYND4
QUICK IQ	-.1054	.1632	-.4981**	-.0895
A	-.1081	.2354	-.3003*	-.1702
ANS	.1137	.3867**	-.1741	-.1675
CIDC	.0274	.2216	-.1910	-.2773
TTC6	.0042	-.0756	.2298	.3348
TTC8	.0105	-.1093	.0597	.1935
CPTE	-.0154	.1018	-.2910*	-.1527
CPTI	-.0437	-.0390	.2751*	-.0804
STPWC	-.0490	-.0470	.2914	.1609
TRLBA	-.0432	.0133	.1888	.2736
CDT	-.0960	-.0821	-.2023	-.1123
CPR	.0343	.1954	-.2662*	.0009
CSR	.0650	.1861	-.2485*	.0252
DF	.0525	.2612*	-.3893**	-.0998
DB	.0573	.1288	-.4506**	-.1924
RPT	.0083	.2547*	-.4530**	-.0104
CML5	.0488	-.1981	.1252	.1470
CRL5	.0276	-.0431	.0676	-.0804
DSS	-.1047	.0095	-.1121	.0142
LAI	.1611	.0674	-.1151	-.0817
SAI	-.0620	-.0560	-.0885	.0055
LINE	.0414	.0340	-.1103	.0224

**P<.01 *P<.05

KEY
A: VERBAL FLUENCY LETTER 'A'
ANS: VERBAL FLUENCY 'ANIMALS'
CIDC: NUMBER OF SUCCESSFULLY COMPLETED STAGES ON THE ID/ED SET SHIFTING TEST
TTC6: TRIALS TO CRITERION ON INTRADIMENSIONAL SHIFT ID/ED SET SHIFTING TASK
TTC8: TRIALS TO CRITERION ON EXTRADIMENSIONAL SHIFT ID/ED SET SHIFTING TASK

CPTE: NUMBER OF CORRECT RESPONSES ON THE CONTINUOUS PERFORMANCE TEST
CPTI: NUMBER OF INAPPROPRIATE RESPONSES ON THE CONTINUOUS PERFORMANCE TEST
STPWC: STROOP TEST WORD-COLOUR CONDITIONS
TLSBA: TRAIL MAKING TEST PARTB-A
CDT: DELAYED MATCHING TO SAMPLE TOTAL CORRECT
CPR: PATTERN RECOGNITION MEMORY TEST
CSR: SPATIAL RECOGNITION MEMORY TEST
DF: DIGIT SPAN FORWARDS
DB: DIGIT SPAN BACKWARDS
RPT: RIVERMEAD BEHAVIOURAL MEMORY TEST PROFILE SCORE
CML5: CANTAB MOTOR TIME STAGE 5
CRL5: CANTAB REACTION TIME STAGE 5
DSS: DIGIT SYMBOL SUBSTITUTION TEST
LAI: LETTER CANCELLATIONASYMMETRY INDEX
SAI: STAR CANCELLATION ASYMMETRY INDEX
LINE: LINE BISECTION INDEX

TABLE 3

CORRELATIONS BETWEEN TOWER OF LONDON PERFORMANCE AND SYNDROME SCORES

	SYND1	SYND2	SYND3	SYND4
CS2	-.0213	.0059	-.2559*	-.1244
CS3	-.0534	.0391	-.2897*	-.1431
CS4	-.0319	.0079	-.3115*	-.1255
CS5	-.0943	-.0493	-.2881*	-.0570
AV2	-.0207	.0156	-.0516	-.1049
AV3	-.1026	.1576	.0329	-.0640
AV4	.0061	.1509	.1685	-.1489
AV5	.1450	.1546	-.0953	-.2216
MI2	-.1856	.1220	.0595	-.0200
MI3	-.2476	-.0450	.0170	-.0500
MI4	-.2758*	.2049	.0893	-.1216
MI5	-.2026	.1023	-.0816	-.0415
MS2	-.2201	.2196	-.0292	.2205
MS3	-.1736	.0701	-.1292	.0533
MS4	-.1662	-.0051	.1718	-.0670
MS5	.1169	.0125	-.0836	.1769
PI2	.2832*	-.0836	-.0755	.0387
PI3	-.0621	.0599	-.0333	-.0526
PI4	-.0947	-.2691*	.0216	-.2037
PI5	-.0616	.0426	-.1291	-.2018
PS2	.0372	-.0197	.1945	.0867
PS3	-.1949	-.1757	-.1045	-.0723
PS4	-.1447	.0267	-.1629	-.0080
PS5	-.1311	.0614	-.2440	-.1040

* P<.05

KEY

CS: COMPLETED SETS

AV: AVERAGE MOVES

MI: MOTOR INITIATION TIMES

MS: MOTOR TIMES SUBSQUENT TO THE FIRST MOVE

PI: PLANNING INTITIATION TIMES

PS: PLANNING TIMES PER MOVE SUBSEQUENT TO THE FIRST MOVE

TABLE 4

PARTIAL CORRELATIONS OF NEUROPSYCHOLOGICAL TEST RESULTS AGAINST SYNDROME SCORES CONTROLLING FOR TAKE AND AIMS RATINGS.

	SYND1		SYND2		SYND3		SYND4	
	TAKE	AIMS	TAKE	AIMS	TAKE	AIMS	TAKE	AIMS
QIQ	-.2240	-.1802	.2636*	.2242	-.4579**	-.4681**	-.0208	-.0408
A	-.1235	-.0572	.3621*	.3161**	-.2506*	-.2753*	-.0575	-.0895
ANS	-.0080	.0332	.3985**	.3289**	-.0922	-.1108	-.1521	-.1730
CIDC	.0657	.0736	-.0972	.1978	-.0972	-.1017	-.2359*	-.2402
TTC6	-.0414	-.0971	.1427	-.0352	.1427	.1666	.2232	.2482
TTC8	-.1063	-.0799	.0142	-.1568	.0142	.0028	.1916	.1773
CPTE	-.0193	-.0587	-.2793*	.0715	-.2793*	-.2560*	-.0995	-.0760
CPTI	.0496	-.0045	.3200**	-.0700	.3200**	.3373**	.0597	.0873
STPWC	.1245	.0698	-.0563	-.0133	.2775*	.2951*	.0827	.1083
TRLBA	.0480	-.0150	-.0718	-.0308	.1787	.2039	.2579*	.2843*
CDT	-.1667	-.1220	-.1876	-.2104	-.1178	-.1351	-.0537	-.0764
CPR	.0602	.0358	.1960	.1937	-.2941*	-.2825*	-.0641	-.0522
CSR	.0440	.0881	.2521*	.2073	-.2155	-.2335*	.0283	.0019
DF	.1292	.1460	.3489**	.3155**	-.4171**	-.4231**	.0059	-.0064
DB	.0618	.1021	.2358*	.1716	-.4230**	-.4343**	-.0860	-.1095
RPT	-.0870	-.0704	.2612*	.2187	-.4373**	-.4430**	.0041	-.0062
CML5	.0131	.0472	-.2667*	-.2620*	.0047	-.0112	.2192	.2030
CRL5	-.0097	.0165	-.0503	-.0555	.0608	.0481	-.1043	-.1170
DSS	-.2068	-.1525	.0067	-.0031	.0039	-.020	.2111	.1849
LAI	.1940	.1703	.0523	.0555	-.1827	-.1727	-.2406*	-.2288*
SAI	-.0958	-.0892	-.0028	-.0300	.0008	-.0021	.0395	.0349
LINE	.0179	-.0019	.1403	.1239	-.0691	-.0609	.0607	.0695

*P<.05 **P<.01

TABLE 5

TOWER OF LONDON PARTIAL CORRELATIONS WITH SYNDROME SCORES WITH RESPECT TO TAKE AND AIMS SCORES

	SYND1		SYND2		SYND3		SYND3	
	TAKE	**AIMS**	**TAKE**	**AIMS**	**TAKE**	**AIMS**	**TAKE**	**AIMS**
AV2	-.0884	-.0857	.0307	-.0664	-.1730	-.1748	.0098	.0095
AV3	-.1930	-.1688	.0723	.1218	-.0025	-.0202	.1678	.1967
AV4	.0763	.0499	.0928	.1164	.3016*	.3156*	.0201	.0329
AV5	.1192	.0774	.1136	.1324	-.0998	-.0746	-.1385	-.1264
MI2	-.2167	-.2424	.0110	.0344	-.0852	.0702	-.1658	-.1519
MI3	-.2422	-.2665*	-.0662	-.0860	.0473	.0598	-.0560	-.0672
MI4	-.2564*	-.2923*	.1856	.2071	.0713	.0918	-.1326	-.1180
MI5	-.2306	-.2346	.1179	.0951	-.0702	-.0695	-.0347	-.0463
MS2	-.2380	-.2701	.2332	.2149	-.0886	-.0732	.2050	.1959
MS3	-.0976	-.1161	.0304	.0594	-.1316	-.1204	.0589	.0738
MS4	-.3305*	-.3423**	-.0669	-.0552	-.0299	-.0251	-.1258	-.1196
MS5	.1400	.1354	.0001	.0173	-.0962	-.0930	.1716	.1802
PI2	.2668*	.2584*	-.0414	-.0765	.0330	-.0224	.2251	.2071
PI3	-.0635	.0036	.0167	-.0083	-.0148	-.0558	-.0465	-.0578
PI4	-.1462	-.0715	-.2623	-.2813*	.0393	-.0046	-.2310	-.2388
PI5	-.0673	-.1220	.0466	.0247	-.1282	-.0999	-.2012	-.2175
PS2	.0548	.0581	-.1031	-.1290	.1410	.1397	.1752	.1601
PS3	-.2315	-.2288	-.2760*	-.2769*	-.1003	-.1038	-.0005	.0200
PS4	-.0571	-.0830	.0152	.0349	-.2065	-.1910	-.0523	-.0416
PS5	-.0836	-.1326	.0282	.0631	-.2849*	.2499	-.1249	-.1034

*P<.05 **P<.01

TABLE 6

DEMOGRAPHICS OF CHRONIC SCHIZOPHRENIC PATIENTS VERSUS CONTROLS (means and sds)

	CHRONICS	CONTROLS	SIGNIFICANCE
SEX (M:F)	48:18	13:12	LR=3.41 df=1 p=.065
AGE (yrs)	40.0 (10.7)	34.1 (13.6)	t=-1.43 df=89 p=.156
EDUCATION (yrs)	11.9 (2.4)	13.4 (2.8)	t=2.61 df=89 p=.011
NART (WAIS equivalent))	107.9 (10.6)	110.6 (10.2)	t=1.07 df=87 p=.288
QUICK IQ	102.1(17.5)	107.4(14.3)	t=1.35 df=88 p=.180
ILLNESS DURATION (yrs)	14.7(11.3)		
ADMISSION DURATION (mths)	84.5(10.7)		
No. ADMISSIONS	10.7(2.3)		
NEUROLEPTICS AT TEST (cpz eq.) mg daily	513(476)		
ANTICHOLINER-GICS AT TEST (procyclidine eq.) mg daily	7.1(6.3)		

TABLE 7

EXECUTIVE TEST PERFORMANCE FOR CHRONIC SCHIZOPHRENIC PATIENTS VERSUS CONTROLS (means and sds)

			WITH EDUCATION					
	CHRONICS n=58	**CONTROLS n=23**		**F**	**P**		**F**	**P**
TEST			**MANOVA df (1,79)**	5.06	.000	**MANOVA df (1,78)**	4.27	.000
A	8.3(4.0)	11.7(3.9)		12.17	.001		6.89	.010
ANS	14.6(5.0)	20.8(5.2)		24.96	.000		18.77	.000
CIDC	6.5(2.9)	8.6(.8)		11.00	.001		7.04	.010
TTC6	22.6(19.9)	7.3(2.8)		13.40	.000		9.73	.003
TTC8	31.8(20.0)	22.4(18.0)		3.85	.053		1.84	.179
CPTE	8.9(2.0)	9.9(.3)		5.14	.026		3.92	.051
CPTI	2.5(2.8)	.7(.9)		8.95	.004		6.12	.016
STRPWC	36.2(26.4)	6.9(9.8)		26.66	.000		19.47	.000
TRLSBA	66.3(45.4)	28.2(14.5)		15.48	.000		9.90	.002

KEY:

A: VERBAL FLUENCY LETTER 'A'
ANS: VERBAL FLUENCY 'ANIMALS'
CIDC: ID/ED SET SHIFTNG NUMBER OF SUCCESSFULLY COMPLETED SETS
TTC6: TRIALS TO CRITERION ON THE INTRADIMENSIONAL SET SHIFTNG TASK
TTC8: TRIALS TO CRITERION ON THE EXTRADIMENSIONAL SET SHIFTNG TASK
CPTE: NUMBER OF CORRECT RESPONSES ON THE CONTINUOUS PERFORMANCE TASK
CPTI: NUMBER OF INAPPROPRIATE RESPONSES ON THE CPT
STRPWC: STROOP WORD-COLOUR CONDITIONS
TRLSBA: TRAIL MAKING TEST PART B-A

TABLE 8

PROPORTION OF CHRONIC SCHIZOPHRENIC PATIENTS AND CONTROLS SUCCESSFULLY PASSING EACH STAGE OF THE ID/ED SET SHIFTING TASK

STAGE	CHRONICS n=63(100%)	CONTROLS n=25(100%)	LIKELIHOOD RATIO	PROBABILITY
1	61(97)	25(100)	1.36	.244
2	59(94)	25(100)	2.75	.097
3	53(84)	25(100)	7.18	.007
4	53(84)	25(100)	7.18	.007
5	50(79)	25(100)	9.56	.002
6	42(69)	24(96)	10.37	.001
7	32(59)	24(96)	14.71	.000
8	29(46)	19(76)	6.77	.009
9	28(44)	19(76)	7.47	.006

TABLE 9

PERFORMANCE ON THE TOWER OF LONDON TEST NUMBER OF COMPLETED SETS FOR CHRONIC SCHIZOPHRENIC PATIENTS VERSUS CONTROLS (MEANS AND SDS)

						WITH EDUCATION		
	CHRONICS n=60	**CONTROLS n=25**		**F**	**P**		**F**	**P**
SET			**MANOVA df (1,83)**	1.44	.228	**MANOVA df (1,82)**	.94	.447
2	1.9(.4)	2.0(.0)		1.28	.260		.76	.387
3	1.9(.5)	2.0(.0)		1.64	.204		.88	.351
4	3.7(1.1)	4.0(.0)		2.19	.142		1.23	.270
5	3.4(1.3)	4.0(.0)		5.38	.023		3.39	.069

TABLE 10

PERFORMANCE ON THE TOWER OF LONDON TEST AVERAGE MOVES TAKEN TO COMPLETE SETS FOR CHRONIC SCHIZOPHRENIC PATIENTS VERSUS CONTROLS (MEANS AND SDS)

						WITH EDUCATION		
	CHRONICS n=56	**CONTROLS n=25**		**F**	**P**		**F**	**P**
SET			**MANOVA df (1,79)**	3.93	.006	**MANOVA df (1,78)**	3.19	.018
2	2.1(.4)	2.1(.4)		.72	.398		.57	.451
3	3.8(1.2)	3.2(.4)		6.61	.012		5.93	.017
4	5.8(1.3)	5.7(1.0)		.14	.711		.09	.763
5	8.3(2.0)	6.9(1.4)		8.93	.004		6.68	.012

TABLE 11

TOWER OF LONDON MOTOR INITIATION TIMES FOR CHRONIC SCHIZOPHRENIC PATIENTS VERSUS CONTROLS (MEANS AND SDS in ms)

						WITH EDUCATION		
	CHRONICS n=47	**CONTROLS n=24**		**F**	**P**		**F**	**P**
SET			**MANOVA df (1,69)**	2.58	.046	**MANOVA df (1,68)**	2.00	.104
2	2461(2052)	1694(1140)		2.93	.091		1.85	.178
3	2267(1506)	1279(391)		9.93	.002		7.70	.007
4	2225(1767)	1397(520)		5.01	.028		3.65	.060
5	2288(1662)	1406(504)		6.42	.014		4.42	.039

TABLE 12

TOWER OF LONDON MOTOR TIMES SUBSEQUENT TO THE FIRST MOVE FOR CHRONIC SCHIZOPHRENIC PATIENTS VERSUS CONTROLS (MEANS AND SDS in ms)

						WITH EDUCATION		
	CHRONICS	**CONTROLS**		**F**	**P**		**F**	**P**
SET			**MANOVA df (1,69)**	6.94	.000	**MANOVA df (1,68)**	5.79	.000
2	1501(531)	1063(563)		10.39	.002		7.69	.007
3	1936(840)	1225(279)		16.16	.000		12.85	.001
4	2070(594)	1364(380)		27.94	.000		23.41	.000
5	2878(6056)	1394(3010		1.43	.236		1.00	.320

TABLE 13

TOWER OF LONDON TEST INITIAL PLANNING TIMES FOR CHRONIC SCHIZOPHRENIC PATIENTS VERSUS CONTROLS (MEANS AND SDS in ms)

						WITH EDUCATION		
	CHRONICS	CONTROLS		F	P		F	P
SET			MANOVA df (1,69)	2.07	.095	MANOVA df (1,68)	1.88	.125
2	2320(2105)	1498(938)		3.31	.073		3.70	.078
3	4506(3379)	3072(2115)		3.59	.062		2.86	.095
4	5417(6681)	3893(2287)		1.17	.283		1.43	.236
5	4519(3393)	5424(3881)		1.02	.315		.87	.354

TABLE 14

TOWER OF LONDON PLANNING TIMES PER MOVE SUBSEQUENT TO THE FIRST MOVE FOR CHRONIC SCHIZOPHRENIC PATIENTS VERSUS CONTROLS (MEANS ANS SDS in ms)

						WITH EDUCATION		
	CHRONICS	CONTROLS		F	P		F	P
SET			MANOVA df (1,69)	2.39	.060	MANOVA df (1,68)	2.44	.056
2	545(866)	334(443)		1.25	.268		1.81	.182
3	1634(2517)	1494(6075)		.02	.891		.08	.775
4	2457(2134)	1640(1710)		2.64	.108		2.37	.129
5	2526(2503)	1098(1479)		6.60	.012		5.22	.025

TABLE 15
MEMORY TEST PERFORMANCE FOR CHRONIC SCHIZOPHRENIC PATIENTS VERSUS CONTROLS (means and sds)

						WITH EDUCATION		
	CHRONICS n=60	**CONTROLS n=23**		**F**	**P**		**F**	**P**
TEST			**MANOVA df (1,82)**	7.49	.000	**MANOVA df (1,81)**	6.47	.000
CDS	8.7(1.8)	9.6(.9)		5.53	.021		3.90	.052
CD0	7.0(1.7)	8.3(1.2)		12.52	.001		8.61	.004
CD4	6.5(2.1)	8.5(1.3)		18.43	.000		15.50	.000
CD12	5.3(1.8)	8.0(1.6)		43.27	.000		37.46	.000
CPR	17.4(3.1)	21.6(2.4)		32.55	.000		26.72	.000
CSR	13.9(2.7)	16.7(2.0)		19.24	.000		13.66	.000
DF	7.4(1.6)	7.8(1.1)		1.70	.196		.27	.614
DB	4.6(1.9)	5.9(1.4)		9.53	.003		4.30	.041
RPT	17.0(5.6)	22.3(1.9)		20.15	.000		14.32	.000

KEY: CDS: DELAYED MATCHING TO SAMPLE (DMTS) SIMULTANEOUS CONDITION
CD0: DMTS 0 SEC DELAY
CD4: DMTS 4 SEC DELAY
CD12: DMTS 12 SEC DELAY
CPR: PATTERN RECOGNITION MEMORY
CSR: SPATIAL RECOGNITION MEMORY
DF: DIGIT SPAN FORWARDS
DB: DIGIT SPAN BACKWARDS
RPT: RIVERMEAD BEHAVIOURAL MEMORY TEST PROFILE SCORE

TABLE 16

PSYCHOMOTOR TEST PERFORMANCE FOR CHRONIC SCHIZOPHRENIC PATIENTS VERSUS CONTROLS (means and sds)

						WITH EDUCATION		
	CHRONICS n=64	**CONTROLS n=22**		**F**	**P**		**F**	**P**
TEST			**MANOVA df (1,84)**	16.57	.000	**MANOVA df (1,83)**	13.98	.000
CML5(ms)	627(223)	438(130)		14.13	.000		11.30	.001
CRL5(ms)	404(120)	322(36)		9.85	.002		7.43	.008
DSS	37.1(11.4)	57.0(12.8)		47.00	.000		39.3	.000

KEY:

CML5: MOTOR TIME STAGE 5 (FROM CANTAB)

CRL5: REACTION TIME STAGE 5 (FROM CANTAB)

DSS: DIGIT SYMBOL SUBSTITUTION TEST

TABLE 17

CANCELLATION TEST AND LINE BISECTION INDICIES FOR CHRONIC SCHIZOPHRENIC PATIENTS VERSUS CONTROLS (means and sds)

						WITH EDUCATION		
	CHRONICS n=66	**CONTROLS n=23**		**F**	**P**		**F**	**P**
TEST			**MANOVA df (1,87)**	.12	.949	**MANOVA df (1,86)**	.19	.902
LETTER	-.3(.5)	-.4(.7)		.20	.659		.37	.544
STAR	-.0(.5)	-.0(.5)		.01	.930		.11	.735
LINE	-6.0(9.3)	-5.1(7.8)		.17	.682		.04	.844

3.5 DISCUSSION

The factor analysis of symptom ratings of a very large group of chronically ill schizophrenic patients, of a wide range of severity and chronicity, produced four distinct groups or syndromes of related symptoms. The first three syndromes, accounting for the largest percentages of variance in ratings, appeared to closely resemble the syndromes or sub pathologies of schizophrenia as reported by Liddle (1987) and Liddle and Barnes (1990). The association between delusions, hallucinations and suspiciousness/persecution symptoms fit well with Liddle's reality distortion syndrome, here with general delusional behaviour related to paranoid type behaviour . Lack of spontaneity and flow of speech, poor rapport, emotional withdrawal and passive/apathetic social withdrawal resembles Liddle's psychomotor poverty syndrome. However, to describe this group of symptoms as characterising psychomotor poverty may be slightly misleading. Rather this syndrome encapsulates the idea of 'poverty of sociability and affect'. The associations between difficulty in abstract thinking, conceptual disorganisation and stereotyped thinking mirrors Liddle's disorganisation syndrome. A fourth related group of symptoms emerged, characterised by grandiosity and hostility. This syndrome may attest to an additional sub pathology not unearthed by the limitations of Liddle's ratings scales i.e. the Manchester scale (Krawiecka et al., 1977) does not assess the aforementioned symptoms. The presence and association between these symptoms may, therefore, reflect the composition of the comprehensive scale i.e. the PANSS, used in the present study. However, this does not necessarily detract from any meaningful interpretation of such a syndrome. In fact, recently, researchers have argued for the inclusion of symptom

ratings reflecting affective and overarousal dimensions of the illness, which appear to be clinically valid (Liddle et al., 1994). In the present instance, the association may be a product of the kind of symptoms expressed by a significant sub group of patients in the sample i.e. recruited from the treatment resistant study, who might express more florid or 'excitable' behaviour than groups of stabilised chronic schizophrenic patients. Further analysis of this sub population's symptom profiles might clarify this. This fourth syndrome accounted for the smallest level of symptom variance and what may be concluded, at least, is that these type of grandiose symptoms are not related to the symptoms characterised by abnormal experiences, deficit states or disorganisation. These sub syndromes or putative sub pathologies of illness, it must be emphasised, were derived from strictly empirical analysis. The degree of meaning which one must give to each syndrome ought to be dictated by face validity along with an explaination on a cognitive level. An explaination of the composition of the syndromes is warranted by which symptoms can be predicted to coexist having a common cognitive substrate.

Like Liddle and Morris (1991), the present study's reality distortion syndrome was not correlated with executive/'frontal' type test performance. Memory performance was also not significantly correlated which may be surprising as delusions and hallucinations have been associated with fundamental problems in memory functioning (McKenna, 1991; Gray et al., 1991). However, in the present study only episodic memory was assessed, whereas the theory surrounding the generation and use of 'false knowledge' i.e. delusions, has been attributed to an impairment in the semantic memory system (McKenna et al., 1994). Despite this, knowledge of any kind must be

acquired and researchers have highlighted that both semantic and episodic memory systems constitute a highly interactive system themselves (Parkin, 1987). Therefore, the acquisition of new semantic memories depends, in part, on normal episodic memory functioning. Here, however, episodic memory functioning was not associated with the reality distortion syndrome directly, therefore, abnormal experiences would appear to arise out of a more indirect and complex cognitive mechanism. Of course, future research ought to involve specific semantic memory tests to clarify this. Time limitation and the overall size of the test battery dictated preference of the episodic memory assessment, particularly in the light of recent literature implicating an impairment in this system, with various heterogeneous groups of schizophrenic patients (McKenna et al., 1990; Tamlyn et al., 1992). An alternative explaination for the genesis of such symptoms i.e. abnormal experiences, within the context of the other findings in this study, is addressed below.

The poverty of sociability and affect syndrome here expectedly significantly negatively correlated with semantic word production but, however, not with initial letter production. In fact, this syndrome seemed to be characterised rather by poor simple working memory and episodic memory. Surprisingly, perhaps, it was not significantly related to psychomotor ability. We, therefore, have deficit type symptoms, characterised by muted social and expressive functioning, related to short term and long term episodic memory dysfunction, although the verbal fluency correlation might suggest slowing of functioning, as well as a semantic accessing problem. Poor social cognition, in terms of using inappropriate social knowledge, has been implicated in formation of schizophrenic symptoms, especially in the realm of

misinterpreting others social behaviour in terms of intentions and beliefs, resulting in persecutory delusions (Frith, 1992). This inability to represent the intentions and beliefs of others has been termed as lacking a 'theory of mind'. Frith (1992; 1994) has also shown that an inability to represent intentions can apply to individuals' personal goal directed behaviour which might explain the delusional passivity phenomena characteristic of schizophrenic behaviour. However, the inability to correctly assess the intentions of others might go far to explain the deficits in social functioning described in the present study. Frith (1992) also states that the fundamental impairment associated with deficit or negative symptoms is an inability to generate self initiated spontaneous action. Therefore, if an individual has an inability in determining others social behaviour and has difficulties initiating their own social behaviour, poor social relations predictably occur. Within the context of the present results, we might hypothesise that the connection between poor memory functioning and social and affective deficits arises from the inability to either access appropriate social knowledge for present functioning or that the memory dysfunction is developmental and insidious so that appropriate social understanding/knowledge memories have failed to be encoded in the first place. Experimental studies have confirmed that schizophrenic patients display a significant level of 'social naivete' compared to manic patients and depressed patients (Cutting and Murphy, 1990). The case for this lack of social knowledge as resulting from poor developmental social experiences has been supported by Foerster et al. (1991) who found that the chronic negative features of schizophrenia are significantly associated with social difficulties in childhood. It is also interesting that similar social empoverishment has been observed as a fundamental feature of autism, which is usually of early onset, and has been associated with lacking

a 'theory of mind' (Wing and Gould,1979; Frith, 1994). The evidence might suggest that poor episodic memory functioning (and, speculatively, associated semantic memory dysfunction) resulting in poor social cognition and judgement, and social empoverishment, exists at an early stage of development and is an insidious process that affects adult social relations. The evidence would also suggest that poor episodic memory is a central feature of adult schizophrenic functioning and thus might have implications for therapeutic programmes involving social education.

The association between disorganisation and memory dysfunction involving recognition tests, working memory and long term episodic memory was robust despite current global intellectual levels. Only continuous performance test correct responses, from the executive test battery, remained significantly associated with disorganisation, after controlling for current intellectual levels. This lack of association with many of the executive functioning test performances does not support Liddle and Morris (1991) who found strong correlations between Stroop test perfromance, verbal fluency and perseverative errors on the Wisconsin Card Sort Test and their disorganisation syndrome. These results were suggestive of an inability to inhibit the effect of inappropriate mental activity on current functioning. This pattern of results resembles the neuropsychological functioning of patients with frontal lobe lesions (Liddle and Morris, 1991). Instead, in the present study those behaviours traditionally associated with frontal lobe deficits i.e. stereotypy and disorganisation of thinking are related to deficits in memory functioning. This pattern may suggest a form of frontal lobe amnesia as the organisational difficulties seen with frontal lobe patients can have a major effect on either the encoding, storage or retrieval of

information (Shallice, 1988). Before controlling for current intellectual levels, there was some evidence to suggest that the disorganisation syndrome was related to executive or 'frontal' type deficits in the form of verbal fluency (initial letter version) and continuous performance test (CPT) correct and incorrect responding. Correct answers on the CPT were still related to the disorganisation syndrome after controlling for current IQ. Therefore, the memory difficulties related to the disorganisation syndrome may be due to organisational problems involving access to and appropriate use of the memory store. The association between frontal type disorganisation and memory difficulties might also be due to confabulation problems in recall (Grafman, 1985). Further analysis of the content of the patients' recall could clarify if this mechanism exacerbated the poor performance. However, the influence of any executive problems must be subtle as tests involving planning ability and set shifting ability were not directly related to the disorganisation syndrome, which is surprising with regard to the latter when stereotyped thinking was a constituent symptom of the syndrome.

After controlling for extrapyramidal side effects, the patterns of the relationships between syndromes and neuropsychological functioning were similar but exaggerated. This was quite surprising as one would expect movement disorders to be associated with impaired functioning, especially in the executive or 'frontal' domain (Brown et al., 1991). Reality distortion was still not significantly related to neuropsychological functioning, as a whole, as was grandiosity. The pattern of significant correlations for poverty of sociability and affect and disorganisation appeared to resemble significant associations with current intellectual levels, executive functioning characterised by verbal fluency and the inability to suppress inappropriate

material and memory functioning involving short term working memory and episodic memory. However, these more marked associations could be products of current levels of intellect, therefore, the associations on preliminary analysis were seen as more conservative and had been dissociated from current levels of intellectual ability, and thus more valid indicators of the connection between syndromes and neuropsychological functioning.

In summary, it appears that, despite Liddle and Morris (1991) findings, in the present study, the emergent syndromes of poverty of sociability and affect and disorganisation are rather more robustly related to poor memory functioning than executive/'frontal' dysfunction. However, in accordance with Liddle and Morris (1991), there was some evidence to implicate some degree of executive association with both syndromes. and that the possibly expected association between reality distortion and memory dysfunction did not materialise.

The neuropsychological performance of the chronic group was robustly inferior to normal healthy controls on executive, memory and psychomotor functioning but not on tests of hemispatial neglect. The latter may be due, in part, to the 'normalising' of left hemispheric functioning after long periods on neuroleptics (Tomer and Flor-Henry, 1989). This pattern remained even after accounting for the poorer educational background of the patients. This extremely marked deficit in functioning domains of the chronic sample was seen in the light of the schizophrenic patients showing pre morbid and current intellectual levels of functioning well within normal limits. The patients, therefore, showed domain specific neuropsychological dysfunction

while experiencing intact global intellectual ability. This contrasts with studies that have demonstrated a decline in intellectual ability in chronic schizophrenic patients (Nelson et al., 1990) but fits in with models of execuitve and memory dysfunction, in schizophrenia, that exist disproportionate to current IQ and/or global cognitive ability (Saykin et al., 1991, McKenna et al., 1990, Tamlyn et al., 1992). However, in the present study the relationship between neuropsychological dysfunction and symptoms appeared more selective. Memory dysfunction was particularly associated with the sub syndromes or pathologies generated with the large group of patients, especially poverty of sociability and affect and disorganisation. Thus, the executive dysfunction expressed by the group appeared to be independent of the expressions of related symptoms. This would call into question the emphasis previous research has had on frontal type functioning in the manifestation of schizophrenic behaviour. The present results would suggest that although groups of schizophrenic patients may show extremely marked deficits in executive functioning it is memory problems that appear to be more associated with symptom expression. With the recent interest in memory dysfunction and schizophrenia (McKenna et al., 1990; Tamlyn et al., 1992), a pattern may be emerging that memory problems are more directly responsible for the organisation and coping strategies needed for purposeful behaviour and that frontal type problems play an adjunctive role in this manifestation (see Saykin et al, 1991).

Delusions and hallucinations and grandiose behaviours, therefore, do arise not as a direct result of neuropsychological dysfunction but rather from cognitive problems associated with abnormal beliefs and social reasoning with neuropsychological dysfunction, perhaps, playing a complementary role

by magnifying stressors or depriving individuals of the abilities essential for coping with them (Bentall, 1994). The cognitive processes responsible for these types of syndromes may be, therefore, understood in terms of cognitive biasing, rather than deficts, underpinned by gross neuropsychological deficits, but also implying that personal and environmental factors have a major part to play in the formation and maintainance of abnormal experiences. The data in the present study cannot confirm the influence of such factors, however, Bentall (1994) suggested a model in which paranoid delusional behaviour and grandiose behaviour may be different manifestations of self serving protective behaviour that helps an individual cope in a threatening environment. The perceived threat arises from a continual catalogue of negative experiences throughout an individual's life. Therefore, in an attempt to preserve self esteem, persecutory delusions and grandiose behaviour result to reduce the attribution of such experiences to the self. It is of note that both these two syndromes could not be explained by neuropsychological performance profiles alone in the present study, and, with regard to reality distortion, had not been in similar previous analyses of syndrome expression with neuropsychological performance e.g. Liddle and Morris (1991) and Brown and White (1992). Therefore, further study is warranted that analyses such abnormal experiential behaviour in context of schizophrenic individual's environment and personal histories along with the neuropsychological deficits, characteristic of chronically ill schizophrenic patients, in a wider appreciation of the cognitive mechanisms that underpin such behaviours.

CHAPTER 4: NEUROPSYCHOLOGY, SYMPTOMS AND ACUTE SCHIZOPHRENIA

4.1 Introduction

It has long been established that patients diagnosed as schizophrenic perform poorly on a range of tests of cognitive functioning (Kolb and Wishaw, 1983). Because of the variable expressions of the illness, it is extremely difficult to derive any understanding of which cognitive impairments underpin which symptoms of the illness through group studies involving heterogeneous samples of patients who happen to have the blanket diagnosis of schizophrenia. Researchers have deemed it necessary to either classify patients into relevant subgroups of the condition according to treatment response (May et al., 1988), or to dispense with group characteristics and analyse the nature of symptom expression individually (see Bentall, 1988) or by analysing related symptom patterns or subsyndromes of the illness (Crow, 1980; Liddle, 1987). The purpose of which is to clarify which particular facets of cognitive dysfunction underlie particular symptoms or 'sub-syndromes' of related symptoms. Studies have shown that patients expressing the positive features of schizophrenia perform better than those with predominantly negative symptoms, across a wide range of tests (Andreasen and Olsen, 1982). However, seeing schizophrenia as a simple dichotomy of symptom profiles does not appear to account for the observed variation in symptom profiles or cognitive performance (Liddle, 1987). Liddle (1987) and Liddle and Barnes (1990) suggested that the heterogeneous nature of schizophrenia arises from the occurrence of

particular pathological processes possibly associated with some fundamental abnormality, peculiar to schizophrenia as a distinct disease entity, rather than expressions of distinct illness types. The different pathological processes ought to have particularly related sets of symptoms or syndromes that can coexist in an individual to differing degrees depending on environmental and/or constitutional factors. Such a system of potentially coexisting differing dimensions of psychopathology had been previously proposed by Crow (1980), although this was based on the traditional positive (acute phase) and negative (chronic phase) dichotomy, encompassing the problems cited above and highlighting the potential to confuse symptom profiles and stages of the illness.

Liddle (1987) and Liddle and Barnes (1990) tried to clarify the relations between symptoms, by factor analysis of symptom profiles, in order to produce empirically derived syndromes of the illness. The authors were able to segregate the symptoms, from samples of stable chronic schizophrenic patients, into three factors or sub syndromes of illness. Firstly, their self-termed 'psychomotor poverty' syndrome was characterised by poverty of speech, flatness of affect and decreased spontaneous movement. The 'disorganisation' syndrome was associated with thought disorders and inappropriate affect. Lastly, delusions and hallucinations were associated as a 'reality distortion' syndrome. Other researchers have been able to produce similar three syndrome analyses of symptom profiles with similar samples of patients (Johnstone et al., 1991; Brown and White, 1992).

As an extension of this syndromic approach, Liddle and Morris (1991) attempted to assess the nature of their emergent syndromes in terms of

cognitive performance. Psychomotor poverty was related to slowness of mental activity (including word generation) while disorganisation was characterised by the inability to inhibit established but inappropriate responses. Reality distortion was not significantly related to performance on any of the cognitive tests provided. Brown and White (1992) found psychomotor poverty to be associated with an impairment on a range of 'frontal' or executive tests but, was also significantly related to tardive dyskinesia and drug induced Parkinsonism. The same authors had previously shown that tardive dyskinesia was, on its own, associated with frontal lobe or executive deficits (Brown et al., 1991). However, the neuropsychological results remained significant after controlling for the presenting extrapyramidal side effect ratings. Disorganisation and reality distortion were not related to psychometric test results, which in the case of the former does not support Liddle's results. The batteries of tests used in the above studies concentrated on the well documented evidence for 'frontal' or executive type deficits seen in schizophrenia (Shallice et al., 1991). The present study aimed to expand the appreciation of other more recently implicated areas of functioning to provide a wider appreciation of the variation and integration of cognitive deficits putatively responsible for schizophrenic symptomatology i.e. memory dysfuction (McKenna et al., 1990; Tamlyn et al., 1992; Saykin et al., 1991).

A feature of the above studies is that only stable chronic patients were used. David (1992) criticised the sole use of such patients in this type of investigation as chronic schizophrenic patients are well known to show cognitive impairment on nearly all types of testing, along with apathy towards prolonged testing that might affect performance. In addition, to

solely use stable chronic patients is to avoid those patients who, having experienced florid periods of illness, do get better. Therefore, the chronic group studies are somewhat biased and do not count for the wide range of illness types, and heterogeneous outcome, seen under the schizophrenia umbrella. As indicated above, it would be safe to assume that patients in the early stages of the illness or patients with acute exacerbation's of symptoms may well express different symptom profiles than chronic stable patients and, therefore, possibly different cognitive performance profiles. The aims of the present study were:

a) to factor analyse symptom profiles of a group of schizophrenic patients in the subchronic phase of the illness or patients with acute exacerbation's of the illness.

b) In order to assess the nature of the pathological processes involved in the illness at this stage, any emergent factors were related to neuropsychological functioning. This study was a preliminary analysis of the nature of florid symptomatology as the numbers of patients used was relatively small with regard to the demands of the statistical methods employed. Of course, it was also necessary to establish the pattern of neuropsychological test performance exhibited by the acutely ill patients against healthy controls to assess dysfunction in this group from the norm.

The cognitive analysis of this group was determined by theoretical considerations of the nature of primarily positive symptomatology. The cognitive impairments putatively associated with negative or deficit symptoms were also assessed due to the observation that different

syndromes of illness can co-exist at any point in the illness process (Crow, 1980). The types of tests used in the present study followed, in part, the considerations of the recent work of researchers such as Gray et al (1991), who proposed a comprehensive neuropsychological model of the positive symptomatology of schizophrenia as being characterised by a 'failure to integrate stored memories of past regularities of perceptual input with ongoing motor programs in the control of current perception' (p.1.). This type of cognitive impairment, it is suggested, results in ambiguous and unstructured sensory input. In this context, thought disorder can be seen as the weakening of moment by moment associations between elements in discourse resulting in abnormal associations (Gray et al., 1991). Hemsley (1987) implied that hallucinations resulted from the inability to inhibit the emergence of material from long term memory resulting in ambiguous messages entering consciousness and then attributing this to an external source. A deficit in the appropriate awareness of knowledge in current perception is implied in the work of Frith (1992), where various internally generated actions are perceived as external in origin due to a failure to monitor one's own intentions ('source memories' or 'memories for action'). Such impairments may give rise to positive symptoms charactersied as passivity phenomena. Frith (1992) has also offered an explaination of negative symptomatology as an inability to generate goal directed behaviour. Therefore, accounting for the theoretical bases of the above models, in the present study tests of inhibition, the ability to carry out goal directed planning and, as indicated above, memory tests were included. Psychomotor functioning was also assessed with respect to abnormal involuntary movement disorders and extrapyramidal side effects in light of the

psychomotor poverty syndrome characteristics of the studies with chronic patient groups so far.

4.2 METHOD

4.2.1 Subjects

Twenty six subjects, (22 males and 4 females) with DSM-IIIR (American Psychiatric Association, 1987) diagnoses of either schizophreniform psychosis (7), subchronic schizophrenia (15) or chronic schizophrenia with acute exacerbation (4), were recruited. The patients were either in- or out-patients of the Royal Edinburgh Hospital. Twenty five controls (13 males, 12 females) were also tested on the neuropsychological measures. All patients and controls were screened for alcohol and/or drug abuse, history of head injury, and for the patients, history of ECT in the previous six months. None of the controls had any history of psychiatric problems whatsoever. Age, sex and number of full time years of education are recorded (see table 1) for both groups. Table 1 also provides group information for the length of schizophrenic illness, number of in-patient admissions to a psychiatric hospital and duration of hospitalisations. Lifetime exposure to neuroleptic medication and the average maximum dose is also provided calculated in chlorpromazine equivalents following the procedure of Rey et al. (1989). Sixteen patients were on neuroleptic medication at testing, 15 on medication that could be calculated in CPZ equivalents, one female patient was also taking 1200mg lithium daily and one male patient was solely on 200mg Clozapine daily. Sixteen patients were taking anticholinergic medication at testing.

4.2.2 Psychiatric Ratings

All patients were assessed on the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1989) to cover a wide range of positive and negative symptom ratings. Full details are given in the main Methods chapter. The patients were also assessed on the Abnormal Involuntary Movement Scale (AIMS; US Department of Health, Education and Welfare, 1976) and the Targeting Abnormal Kinetic Effects (TAKE) scale (Wojcik et al., 1980) for evidence of tardive dyskinesia and parkinsonian side effects, respectively, at interview. All psychiatric ratings and movement disorder scales were carried out with the collaboration of experienced and trained psychiatrists.

4.2.3 Neuropsychological Measures

Both the acutely ill patients and the control group were tested on a battery of neuropsychological tests designed to clarify the cognitive deficits that may underlie those symptoms that characterise a group of florid and acutely ill patients with a diagnosis of schizophrenia.

General intellectual functioning was measured by using the National Adult Reading Test (NART) (Nelson, 1982) as an index of pre morbid ability. Current intellectual ability was measured with the Quick Test (Ammons and Ammons, 1962) and general cognitive functioning by use of the Mini Mental State Examination (MMSE) (Folstein et al., 1975; Dick et al., 1984).

Executive functioning was measured by using a verbal fluency task (FAS and Animal categories) (from Spreen and Strauss, 1991), a cognitive estimation task (Shallice and Evans,1978), a computerised continuous performance task (Frith et al, 1991), the Stroop test (Trenerry et al., 1989) and the Trail Making Task (A&B) (Reitan, 1958). Two further computerised tests of executive functioning were administered from the CANTAB (Robbins et al., 1991); the Intra/Extradimensional Set Shifting task and the Tower of London task- a measure of planning ability.

Memory functioning was measured using the Auditory Verbal Learning Test (AVLT) (Rey, 1964), the Rivermead Behavioural Memory Test (RBMT) (Wilson et al., 1985), Hebbs Recurring Digits test (Milner, 1970), the Silly Sentences test (Collins and Quillian, 1969). A computerised Delayed Matching to Sample task was also administered from the CANTAB (Robbins et al., 1991).

Psychomotor functioning was assessed using the reaction and motor time measure from the CANTAB and the Digit Symbol Substitution Test (from the WAIS-R, Wechsler, 1981).

Details of the administration and scoring of all the above tests with theoretical backgrounds can be seen in the main Methods chapter.

All subjects were tested at one sitting, if possible, if not all were done on the same day with convenient breaks. The psychiatric ratings and movement disorder scales were carried out on the same day as testing (+/-1).

4.2.4 Data Analysis

Factor analysis was undertaken with rating scores of the 14 symptoms (7 positive, 7 negative) from the PANSS scale (for specific symptoms see Methods). Analysis was similar to that carried out by Liddle and Barnes (1990). Initial factors were extracted by the method of principal components. An oblique rotation was performed as there was no a priori evidence that symptoms should be related. Factor scores were calculated by the regression method. All analyses were performed using SPSS 4.0 on a Macintosh personal computer.

Pearsons correlations (two-tailed) were used between factor scores and neuropsychological test results of the acutely ill schizophrenic patient group. Correlations were also performed between factors and education background, illness duration, length of hospitalisations, duration of antipsychotic medication and neuroleptic and anticholinergic medication at interview. The movement disorder scale totals were also analysed with respect to the emergent factors by correlation.

To analyse the pattern of the acutely ill schizophrenic patient group's neuropsychological test performance, their results were compared with the control group. Test performance between the two groups was analysed by combining the measures into groups by function i.e. executive function performance, memory performance. Comparison was calculated using the multivariate analysis of variance (MANOVA) to assess any overall effects by function. Group means were used to account for missing data. In the case of test results, with expected missing data due to the design of the test i.e.

fewer subjects reaching the more difficult stages of the ID/ED Set Shifting Task, t-tests (two tailed) were used to analyse group differences. Chi squared statistics were used to analyse the proportion of subjects per group reaching each stage of the Set Shifting Task.

4.3 RESULTS

4.3.1 Factor Analysis (see table 2)

Five factors emerged having an eigenvalue greater than one. These factors accounted for 75.8% of the variance. Factor 1 accounted for 33.6% of the total variance loaded highly on hostility, excitement, suspiciousness/persecution, stereoptyped thinking poor rapport and hallucinations. Such a syndrome comprises related symptoms characteristic of a state of paranoia. This is the most prevalent syndrome in this particular group of patients. Factor 2, accounting for 16.5% of total variance, loaded negatively but highly on emotional withdrawal and blunted affect. This syndrome appears to signify poverty of emotional functioning or affect. Factor 3, variance 10.8%, loaded very highly but solely on grandiosity. Factor 4, variance 7.7%, loaded highly on conceptual disorganisation, passive/apathetic social withdrawal and stereotyped thinking. Such a syndrome appears to be highlighting aspects of disorganisation and social dysfunction. Finally, the fifth factor loaded highly on delusions alone.

4.3.2 Correlations between demographics, neuropsychological test performance and factors/syndromes (see table 3 for individual correlations)

As the group of patients was relatively small for a factor analysis comprising 14 variables, only correlation levels of significance between the emergent factors and performances at the $p<.01$ level were considered. Very few significant correlations emerged. No significant correlations were found between the Factors and illness duration, full time years of education, length of hospitalisations, lifetime exposure to neuroleptic medication or medication (antipsychotics and anticholinergics) at time of interview. There were no significant correlations with either movement disorder scale.

Factor 4, 'disorganisation and social dysfunction', was significantly negatively correlated with completed sets on the ID/ED Set Shifting Task. Factor 5, 'delusions', was significantly correlated with errors incurred on the intradimensional and extradimensional shift stages of the ID/ED Set Shifting Task. The only other correlation of note is that between Factor 4 and number of correct responses on the Delayed Matching to Sample Task for the 12 second delay condition.

4.3.3 Neuropsychological test performance of Acute Schizophrenic patients versus Controls

4.3.3.1 Demographics (see table 1)

Firstly, the two groups were not matched for sex ratio. This may not be all that surprising due to the well known imbalance between the sexes experiencing schizophrenia at a young age (Kendell, 1986). Since the acutely ill patients were indeed a young sample, there was a significant difference in mean age between the groups. There was no difference in the number of full time years of education or academic history (LR=9.26 df=4 p=.055) experienced by each group. The two groups did, however, come from differing family backgrounds. The control group came from more privileged backgrounds as measured by paternal occupation (LR=12.82 df=6 p<.05) while there was a greater likelihood that the schizophrenic patients had a relative who had or was suffering the same illness (LR=7.26 df=1 p<.01). There was also no difference between the groups on a handedness scale (LR=.695 df=1 p=.404). The groups did not significantly differ on NART performance, an estimate of pre morbid intellectual functioning.

Because of the difference in ages between the groups all the comparison analyses of neuropsychological test performance were carried out using age as a covariate

4.3.3 2 General Intellectual Performance (see table 4)

There was overall and univariate significant differences in performance on global measures of current intellectual functioning.

4.3.3.3 Executive functioning performance (see table 5)

On initial analysis of the executive tests the overall group difference was just more than the $p<.05$ level of significance, at $p=.069$. With this in mind, univariate analysis showed significantly poorer Stroop performance (word-colour conditions), reaction time on the continuous performance test number correct, the semantic (animals) category on the verbal fluency test and the Trail Making test performances, on behalf of the schizophrenic patients.

The patient grouped performed poorly on the ID/ED Set Shifting Test reaching criteria on fewer stages of the problem than the healthy controls. Similar proportions of patients as controls completed each stage except for 15 patients (58%) against 24 (96%)that successfully completed stage 7 (ID shift reversal) ($LR=8.210$ $df=1$ $p<.01$). There were no group differences on trials to reach criteria on either the intradimensional shift (stage 6) (AX: 16.7(19.5), CX: 9(8.9) $F=3.012$ $df(1,45)$ $p=.09$) or on the extradimensional shift (stage 8) (AX: 22.3(17.6), CX: 22(17.7) $F=.124$ $df(1,38)$ $p=.727$).

The computerised Tower of London task showed no group differences whether considering number of completed sets, number of average moves per set to complete the problem, motor initiation times, planning initiation

times or subsequent planning times (see tables 6 & 7). The patients showed slower movement times subsequent to the first move than did the control subjects.

4.3.3.4 Memory test performance (see table 8)

Overall, the acutely ill patients did not differ significantly from healthy controls on a wide range of memory tasks. Univariate analyses, however, showed the healthy controls performing better on a digits forward task (Hebbs digits), on an episodic memory test (RBMT) and on a test of semantic memory (Silly Sentences test; number correct and error response latency). These univariate differences were at a high level of significance. There was also a trend for the acutely ill patients to score progressively poorer the longer the delay between the target stimuli and choice stimuli on the delayed matching to sample task.

4.3.3.5 Psychomotor ability (see table 9)

The acutely ill patients performed significantly worse on a computerised movement and reaction latency task and also a task of timed visuo-spatial coding (Digit Symbol Substitution Test). There appears to be a great difference in overall psychomotor ability in favour of the healthy controls as assessed on these measures.

TABLE 1

DEMOGRAPHIC VARIABLES FOR ACUTELY ILL SCHIZOPHRENIC PATIENTS AND CONTROLS

	ACUTES	CONTROLS	SIGNIFICANCE
SEX M:F	22:4	13:12	LR=6.507 df(1) p<.05
AGE(yrs)	24(4.6) range 17.1-39.3	34.1(13.6) range 18.4-63.8	t=-3.55 df(49) p<.001
EDUCATION(yrs)	12.4(2.2)	13.4(2.8)	t=-1.44 df(49) p>.1
NART (WAIS EQ.)	106.3(8.7)	110.6(10.0)	t=.661 df(48) p>.1
ILLNESS DURATION (mths)	11.8(16.7)		
ADMISSION DURATION (mths)	3.2(3.7)		
No. ADMISSIONS	2.5(2.7)		
MEDICATION DURATION (mths)	16.5(24.9)		
AV. MAX DOSE (daily CPZ equiv. mg)	414(472)		
ANTICHOLINER-GIC MEDICATION (daily Procyclidine equiv. mg) at test.	3.8(5.3) n=16		
NEUROLEPTIC MEDICATION (daily CPZ equiv. mg) at test	196(300) n=16		

TABLE 2

FACTOR LOADINGS OBTAINED BY FACTOR ANALYSIS OF SYMPTOMS OF A SAMPLE OF ACUTELY ILL SCHIZOPHENIC PATIENTS

SYMPTOMS	FAC 1	FAC 2	FAC 3	FAC 4	FAC 5
HOSTILITY	.864	-.019	-.058	-.016	-.068
EXCITEMENT	.852	.353	.108	.194	-.099
SUSPICIOUSNESS/ PERSECUTION	.823	-.055	-.010	-.121	.230
STEREOTYPED THINKING	.694	-.140	-.009	.448	.032
POOR RAPPORT	.545	-.492	.035	.263	-.017
HALLUCINATIONS	.499	-.350	-.339	-.134	-.409
EMOTIONAL WITHDRAWAL	.346	-.847	.228	-.123	-.132
DIFFICULTY IN ABSTRACT THINKING	.181	.440	-.041	-.023	.054
CONCEPTUAL DISORGANISATION	.174	.148	-.240	.825	-.203
BLUNTED AFFECT	.138	-.777	-.065	-.002	.289
DELUSIONS	.125	-.042	-.140	-.062	.893
GRANDIOSITY	.077	.004	.913	-.017	-.121
PASSIVE/APATHETIC SOCIAL WITHDRAWAL	-.108	-.238	.282	.682	.120
EIGEN VALUE	4.698	2.308	1.516	1.075	1.014
% VARIANCE	33.6	16.5	10.8	7.7	7.2
CUM % VARIANCE	33.6	50.0	60.9	68.6	75.8

TABLE 3

CORRELATIONS BETWEEN FACTORS, DEMOGRAPHICS AND NEUROPSYCHOLOGICAL TEST SCORES OF ACUTELY ILL SCHIZOPHRENIC PATIENTS

DEMOS.	FACTOR 1	FACTOR 2	FACTOR 3	FACTOR 4	FACTOR 5
ILLNESS DURATION	-.2652	.4449*	.0520	.1692	.0603
EDUC.	-.1481	.0439	.0348	-.1489	-.1081
DURATION OF ADMINS.	-.4206	-.1477	.0948	-.0346	-.1738
NEUROLEP-TIC DURATION	-.4101*	.0225	.0706	.0591	-.1003
NEUROLEP-TIC LEVELS AT TESTING	-.3857	-.3176	-.1626	-.0761	-.0828
ANTICHOLI-NERGIC LEVELS AT TESTING	-.3842	-.3151	-.2059	-.1336	-.0860
AIMS TOTALS	.0018	-.0180	.3037	-.0030	.0188
TAKE TOTALS	-.4051	-.2528	.1932	.1336	.1434
TESTS					
F	.0011	-.2644	.3184	-.1959	.0349
A	-.3184	.2210	.1163	-.0435	-.0603
S	-.0963	.0320	.1124	-.0506	-.1931
ANS	-.2254	.1944	.1808	.0194	-.1226
COG EST.	.0165	.0460	-.1504	.1555	-.0745
STROOP	.0168	.1655	-.3475	.4183*	.0750
TRLSB-A	.0010	.0855	-.3035	.1669	-.1225
CPTI	-.1311	.0076	-.0106	.3174	-.0864
CPTIRT	-.0630	-.2765	-.2514	.3072	.4905*
CPTE	.2933	.2944	.0321	-.1224	.0638
CPTERT	-.2080	-.1921	-.1118	.1494	.2579

TEST	FACTOR 1	FACTOR 2	FACTOR 3	FACTOR 4	FACTOR 5
ID/ED					
SETS	.0816	.4365*	-.0060	-.5483**	-.1786
TTC ID	-.0820	-.2140	-.2323	.2160	.3717
TTC ED	.3690	-.4663	-.0391	.4474	.5950
ERR ID	.1023	-.1484	-.1422	.2651	.6455**
ERR ED	.3610	-.4678	.0370	.4858	.6467**
TOWER					
AV MOVE2	-.1300	.0227	-.1043	.1558	-.1726
AV MOVE3	-.2323	-.1513	-.2441	.0812	-.1579
AV MOVE4	.0055	.0835	.5956**	-.0240	-.1284
AV MOVE5	.1541	-.0161	-.4005	-.2427	.0849
MOTORIT2	.1019	-.3481	-.1199	-.0877	.0239
MOTORIT3	-.3745	-.4131	-.1887	.0351	.0209
MOTORIT4	-.2065	-.3652	-.1084	.1586	.0014
MOTORIT5	-.2509	-.2694	-.1028	.2066	-.0863
MOTORST2	.1019	-.3481	-.1199	.0877	.2239
MOTORST3	.3745	-.4131	-.1887	-.0357	.0209
MOTORST4	-.1206	-.3200	-.2659	.2687	.1806
MOTORST5	-.1037	-.2204	-.3156	-.1227	-.1774
PLANIT2	-.1184	-.1491	-.1838	-.0447	-.2630
PLANIT3	.4844*	-.3012	.2456	-.2106	-.2411
PLANIT4	.0943	-.0597	-.0648	-.2049	-.2455
PLANIT5	-.1454	.2484	.2261	.5249*	-.0266
PLANST2	.0491	-.1727	-.1856	.0252	-.3133
PLANST3	.0975	.0640	-.0740	-.0645	-.1395
PLANST4	.2502	-.2216	-.0488	-.0879	-.2527
PLANST5	.2022	-.1950	.0727	-.1038	-.0415

TEST	FACTOR 1	FACTOR 2	FACTOR 3	FACTOR 4	FACTOR 5
AVLT5-6	.3561	-.0089	.0863	-.1452	.3810
HEBS	-.2801	-.2002	.4883*	-.0843	.1489
HEBS LEARN	-.1096	-.0499	-.1032	.3440	.3903*
RBMT PRO	-.3541	-.2604	.1873	-.4474*	.0703
SILLY SENT	.0354	-.0378	.1851	.1675	.0890
SSRT	.0595	.1880	-.0870	-.0021	-.1551
CDMS	.0704	.0120	.0932	-.1052	.2303
CDMSL	-.0376	.0690	.0188	.2721	.3462
CDM0	.1482	-.0986	.1519	-.2228	.1148
CDM0L	-.1806	.1804	.0355	.1795	.3688
CDM4	-.0084	.0227	-.0963	-.1175	.1243
CDM4L	-.0398	.3538	.0979	.3866	-.0288
CDM12	-.0164	-.0521	.0751	-.4969**	-.2015
CDM12L	-.0866	.3139	-.1569	.2035	-.1241
CDMT	.0763	-.0288	.0577	-.3263	.0424
CDMTL	-.0920	.2988	-.0140	.2973	.1333
MOTOR L	.1393	-.3329	-.0970	.1430	-.0781
REACT. L	.0019	.0206	-.2334	-.0998	-.0342
DSSR	.0920	.1797	.3641	-.1399	.0115

KEY:

EDUC. FULL TIME YEARS OF EDUCATION
ANS ANIMALS
COG EST COGNITIVE ESTIMATION TEST
STROOP STROOP TEST WORD-COLOUR CONDITION
TRLSB-A TRAILS PARTB-A
CPTI CONTINUOUS PERFORMANCE TEST INAPPROPRIATE RESPONSES
CPTIRT CPTI REACTION TIME
CPTE CPT CORRECT RESPONSES
CPTERT CPTE REACTION TIME
ID/ED SET SHIFT
SETS NUMBER OF COMPLETED SETS
TTC ID TRIALS TO CRITERION OF STAGE 6 (ID SHIFT)
TTC ED TTC OF STAGE 8 (ED SHIFT)
ERR ID ERRORS TO CRITERION STAGE 6
ERR ED ERR TO STAGE 8
TOWER OF LONDON
AV MOVE 2-5 AVERAGE MOVES TAKEN TO COMPLETE EACH SET
MOTORIT 2-5 INITIATION OF MOTOR TIME RESPONSE
MOTORST 2-5 SUBSEQUENT MOTOR RESPONSE TIME TO THE FIRST MOVE

PLANIT 2-5	PLANNING TIME FOR INITIATING FIRST MOVE PER SET
PLANST 2-5	PLANNING TIME FOR MOVES SUBSEQUENT TO THE FIRST MOVE
AVLT 5-6	AUDITORY VERBAL LEARNING TEST NUMBER CORRECT STAGE 5-6
HEBBS	DIGITS SPAN FORWARDS
HEBBS LEARN	HEBBS STAGES TO LEARN SPAN
RBMT PRO	RIVERMEAD BEHAVIOURAL MEMORY TEST PROFILE SCORE
SILLY SENT	SILLY SENTENCES TEST NUMBER CORRECT
SSRT	SS RESPONSE TIME
CDMS	DELAYED MATCH TO SAMPLE NO DELAY
CDMSL	CDMS REACTION LATENCY
CDM0	CDM 0SEC DELAY
CDM0L	CDM0 REACTION LATENCY
CDM4	CDM 4SEC DELAY
CDM4L	CDM4 REACTION LATENCY
CDM12	CDM 12SEC DELAY
CDM12L	CDM12 REACTION LATENCY
CDMT	CDM TOTAL
CDMTL	CDMT REACTION LATENCY
MOTORL	MOTOR LATENCY ON CANTAB REACTION TIME TEST STAGE 5
REACTL	REACTION LATENCY ON CRT STAGE 5
DSSR	DIGIT SYMBOL SUBSTITUTION TASK FROM WAIS-R

TABLE 4

PERFORMANCE ON MEASURES OF CURRENT GLOBAL INTELLECTUAL FUNCTIONING OF ACUTELY ILL SCHIZOPHRENIC PATIENTS VERSUS CONTROLS WITH AGE (MEANS & SDS).

	ACUTE	CONTROL		F	P
			MANOVA df (1,48)	3.495	.023
QUICKIQ	94.6(13.0)	107.4(14.3)		5.229	.027
MMSE	26.9(3.4)	28.9(2.0)		6.068	.017

TABLE 5

PERFORMANCE ON TESTS OF EXECUTIVE FUNCTIONING OF ACUTELY ILL SCHIZOPHRENIC PATIENTS VERSUS CONTROLS WITH AGE (MEANS & SDS).

	ACUTE	CONTROL		F	P
			MANOVA df (1,48)	1.925	.067
F	11.3(4.8)	13.5(4.0)		3.383	.072
A	9.5(3.2)	11.5(4.1)		2.753	.104
S	12.2(4.0)	14.6(4.1)		4.013	.051
ANIMALS	17.8(5.0)	21.2(5.8)		4.950	.031
COG EST	8.3(6.5)	4.7(5.5)		3.657	.062
TRAILSB-A	51.7(49.6)	32.7(29.4)		4.691	.035
STROOP (word-colour)	26.8(24.5)	6.6(9.5)		13.259	.001
CPTI	1.9(2.0)	.8(.8)		3.832	.056
CPTIRT	585(367)	304(346)		7.188	.010
CPTE	9.8(.8)	9.8(.4)		.709	.404
CPTERT	657(96)	586(148)		8.114	.006

TABLE 6

COMPLETED SETS AND AVERAGE MOVES TAKEN PER SET FOR PERFORMANCE ON THE TOWER OF LONDON TASK OF ACUTELY ILL SCHIZOPHRENIC PATIENTS VERSUS CONTROLS WITH AGE (MEANS & SDS).

	ACUTE	CONTROL		F	P
COMPLE-TED SETS			MANOVA df (1,43)		
2	2(0)	2(0)			
3	2(0)	2(0)			
4	3.9(.6)	4(0)		.954	.334
5	3.8(.8)	4(0)		.954	.334
AVERAGE MOVES			MANOVA df (1,43)	1.497	.221
2	2.1(.3)	2.1(.4)		.317	.576
3	3.6(.8)	3.2(.4)		5.040	.030
4	5.5(1.0)	5.7(1.0)		.236	.630
5	7.3(1.2)	6.9(1.4)		.254	.617

TABLE 7

INITIAL MOTOR AND PLANNING TIMES PER DEGREE OF TASK DIFFICULTY AND SUBSEQUENT MOTOR AND PLANNING TIMES PER MOVE PER DEGREE OF TASK DIFFICULTY FOR TOWER OF LONDON PERFORMANCE OF ACUTELY ILL SCHIZOPHRENIC PATIENTS VERSUS CONTROLS WITH AGE (MEANS & SDS in ms)

	ACUTE	CONTROL		F	P
MOTOR INITIATION TIMES			MANOVA df (1,43)	.754	.594
2	1646(557)	1694(1140)		1.968	.168
3	1332(369)	1277(391)		2.044	.160
4	1570(1108)	1397(520)		1.409	.242
5	1643(1058)	1406(504)		1.938	.171
SUBSEQUENT MOTOR TIMES			MANOVA df (1,43)	3.582	.014
2	1137(294)	1063(563)		2.355	.132
3	1448(434)	1225(279)		7.365	.010
4	1350(390)	1060(276)		14.824	.000
5	1646(482)	1394(301)		8.758	.005
PLANNING INITIATION TIMES			MANOVA df (1,43)	.652	.629
2	2093(2193)	1498(938)		1.654	.205
3	3370(1993)	3072(2115)		.995	.324
4	3747(2769)	3893(2287)		.098	.756
5	4228(4290)	5424(3881)		.630	.432
SUBSEQUENT PLANNING TIMES			MANOVA df (1,43)	.314	.867
2	309(405)	334(443)		.044	.835
3	996(1488)	1494(6075)		.300	.587
4	1419(1064)	1640(1710)		1.083	.304
5	1115(995)	1098(1479)		.557	.460

TABLE 8

MEMORY TEST PERFORMANCE OF ACUTELY ILL SCHIZOPHRENIC PATIENTS VERSUS CONTROLS WITH AGE (MEANS & SDS-reaction latencies in ms)

TEST	ACUTE	CONTROL		F	P
			MANOVA df (1,48)	1.350	.225
AVLT5-6	2.2(2.7)	1.4(1.3)		1.500	.227
HEBBS	7.1(1.10	7.9(1.0)		7.200	.010
HEBBS (L)	4.5(2.3)	3.7(2.0)		.250	.619
RBMT PROFILE	19.5(5)	22.3(1.9)		4.910	.031
SILLY SEN-TENCES	48.1(2.9)	49.8(.6)		6.363	.015
SS RT	842(345)	752(157)		1.847	.180
SS INC RT	1017(1232)	102(288)		11.465	.001
DELAYED MATCH TO SAMPLE					
NO DELAY	9.1(.9)	9.5(1.0)		6.670	.013
RL	3179(659)	2988(773)		4.033	.050
0S DELAY	8.0(1.8)	8.4(1.2)		1.417	.240
RL	2933(598)	3034(842)		.224	.638
4S DELAY	7.4(1.6)	8.6(1.3)		8.549	.005
RL	3563(870)	3214(849)		2.179	.146
12S DELAY	6.3(1.9)	8.2(1.6)		11.907	.001
RL	4096(1043)	3767(1060)		3.418	.071
TOTAL	30.9(4.5)	34.7(3.6)		2.772	.001
RL	3412(640)	3253(761)			.102

TABLE 9

PERFORMANCE ON TESTS OF PSYCHOMOTOR ABILITY OF ACUTELY ILL SCHIZOPHRENIC PATIENTS VERSUS CONTROLS WITH AGE (MEANS & SDS)

	ACUTE	CONTROL		F	P
TEST			MANOVA df (1,48)	5.086	.002
MOTOR LATENCY STAGE 5	581(208)	434(125)		7.444	.009
REACTION LATENCY	388(150)	322(35)		4.780	.034
DIGIT SYMBOL SUBSTITU-TION	44.6(14.10	57.0(12.0)		15.875	.000

4.4 DISCUSSION

The five emergent factors from the present analysis of acutely ill schizophrenic patients' symptoms differed greatly from those derived from studies using samples of stable chronically ill patients e.g. Liddle (1987); Liddle and Barnes (1990); Brown and White (1992). The factors yielded in the present study indicated separate entities of empirically related symptoms characterised by a 'paranoid state', 'poverty of affect', 'grandiosity', 'disorganisation and poverty of sociability' and 'delusions'. The symptoms entered into the factor analysis, therefore, showed different relations than those that composed the 'psychomotor poverty', 'disorganisation' and 'reality distortion' of the above studies. The factors in the present study may, of course, represent nothing more than spurious findings due to the small number of patients' symptoms entered into the factor analysis. The factors are also representative of those symptoms that appear on the rating scale being used. The use of the PANSS scale might, therefore, expose close relations between symptoms some of which have not been entered into previous analyses. The PANSS, however, was used due to its comprehensive inclusion of clinically valid symptomatology and the degree to which the severity of symptoms could be recorded (see Methods). These attributes have been suggested as advantageous in intensive studies of schizophrenic symptomatology over more traditional and limited measures (Kay et al., 1989). It is, therefore, possible that the characteristics of the factors in the present study are a comprehensive representation of the sub syndromes or pathologies of illness at an acute or early phase of illness. The sample of early or acute phase schizophrenic

patients is likely to be comprised of individuals of mixed prognosis i.e. that, after experiencing a single or small number of episodes some patients are likely to recover and not relapse i.e. patients of good prognosis. The samples of chronic patients would comprise only those patients of poor prognosis that have not recovered. Therefore, the comparison of symptom expression between acute and chronic stages of illness ought to consider the differences in patient types that constitute the different groups. In effect, the repeated findings of the three syndrome 'model' of schizophrenic symptoms might be characteristic of poor outcome and thus not representative of the heterogeneous outcomes seen in schizophrenia as a whole. The difference in factor type, between the acute and chronic stages of the illness, might also reflect the instability of individual symptom profiles at an extremely florid early stage of illness. The numbers of patients used in the present study was, however, very small especially with regard to the demands of the statistical analysis used. Thus, any interpretation should regard the present results as a preliminary analysis which might provide direction for future larger studies. The small number of patients used in the present study also attests to the difficulty in the recruitment and completing of relatively demanding psychiatric and neuropsychological assessments of floridly ill patients.

There were very few significant relationships between neuropsychological performance and the emergent factors. In fact, in considering the exhaustive nature of the neuropsychological battery used, the symptom groups appeared independent of any direct underlying cognitive abnormalities. In similar studies involving chronically ill patients 'psychomotor poverty' has been related to slowing of mental activity

(Liddle and Morris, 1991; Brown and White, 1992) and 'disorganisation' has been significantly related with disinhibition (Liddle and Morris, 1991). In these studies the 'reality distortion' sub syndrome has only been related to an impairment in figure-ground perception (Liddle, 1987). In the present study, those dimensions of cognition involving executive, memory and psychomotor functioning, as assessed by the many varied tests used here, failed to uncover any direct underlying cognitive abnormalities that might explain the various sub pathologies of illness at an acute stage. This may be, in part, due to the 'state' nature of the symptom ratings of a highly unstable group of patients whereas the neuropsychological performance of this group could be assumed as more 'trait' like. Thus the continuous variation in acuteley ill patients symptom expression may provide too much 'noise' to show any direct associations with underlying neuropsychological impairments. This may, of course, mean that the empirical relations between symptoms and, therefore, resultant syndromes are unstable and invalid. This possibility must be taken into account during the following interpretation of the study's findings. Despite this, the comparison of the acute patient samples' functioning compared to healthy controls exposed a broad range of cognitive impairment despite equivalent pre morbid functioning levels. There was a difference in sex ratio and age between the groups that is representative of the early stage of illness under investigation, and that males are more likely to experience first onset of illness at a younger age than females (Kendell, 1986).

Despite the age differences between the groups, the acutely ill patients displayed significantly poorer current general intellectual functioning. In the comparison of

executive functioning, the patients showed significant impairments on tests measuring verbal fluency by semantic category, attention shifting and ability to inhibit inappropriate responses and subsequent (to the first move) motor times, especially on the harder tasks of the Tower of London test. However, the groups could not be differentiated on planning ability. The patient sample also showed memory impairments on both short term auditory recall and long term episodic and semantic memory measures. Non verbal recognition memory was also compromised particularly on delay dependent test conditions. Robust overall and univariate differences were exposed on the analysis of the groups' psychomotor functioning. It has already been noted that the acutely ill patients motor times were significantly poorer than the controls in completing the Tower of London tasks. The acutely ill group appears to have major difficulties with speed of cognitive functioning.

The emerging picture, in the present analysis, is one of acutely ill patients showing major cognitive impairments in executive, memory and, particularly, psychomotor functioning. All these areas of neuropsychological functioning have been implicated as characterising schizophrenic functioning, as a whole, usually, with heterogenous samples of patients (see Kolb and Wishaw, 1983; McKenna et al., 1990 and Pantelis et al., 1992). In particular, the present results support the accumulating evidence for memory dysfunction as characterising schizophrenic functioning (McKenna et al., 1990; Tamlyn et al., 1992; Saykin et al., 1991), especially in relation to the formation of positive symptoms e.g. Gray et al. (1991). This is noteworthy as the patients in the present study were charaterised by the florid nature of their illnesses. However, there

appears to be little direct association between such neuropsychological impairments and the sub syndromes of related symptoms expressed at this stage of illness. The expression of illness, in terms of sub syndromes of related symptoms, at the acute stage, appears to be due to more than the direct effects of domain specific cognitive deficits derived from performance on the types of neuropsychological tests, however exhaustive, used in the present analysis. Rather than being independent phenomena, the cognitive deficits, displayed by the patients at this stage, are more likely to be secondary deficits that underpin another primary level of psychological dysfunction more directly related to symptom expression. In any case, if a relation between neuropsychological performance and symptoms had been found, to say that a long term memory impairment 'causes' delusional behaviour does not explain the mechanisms by which the impairment has affected belief acquisition and the use of false knowledge that comprises delusional behaviour. The composition of the sub syndromes of related symptoms, together with the neuropsychological performance data, should point to, at least, a theory of the psychological system that mediates between poor neuropsychological performance and symptom expression. Such an enterprise using the present data might be somewhat ambitious and would require further investigations with more theory driven test materials. However, in the light of recent cognitive models of paranoid delusional behaviour (e.g. Bentall, 1994), that sub syndrome accounting for the greatest variance in the present study, we might speculate as to the mediating processes, underpinned by fundamental cognitive impairments, that give rise to this specific dimension of schizophrenic behaviour.

The present study's 'paranoid state' syndrome comprised of hostility, excitement, suspiciousness/persecution, poor rapport and hallucinations. These symptoms suggest a process of hyperarousal involving persecutory beliefs with concomitant social dysfunction and hallucinations. However, we cannot tell if the hallucinations, in this instance, are paranoid in content, only that they are significantly associated with such symptoms as suspiciousness/persecution. Further studies might benefit from additional qualitative considerations of the symptom types. The formation of paranoid delusions has recently been suggested as due to the schizophrenic patient's cognitive bias in selective information processing that act as a defence against low self esteem (Bentall, 1994). Richard Bentall's model of the formation of paranoid delusions involves the consideration of an individual's place in the social environment, as well as neuropsychological processes, based on the assumption that this type of delusion shows intentionality. In essence, the environmental experiences of the schizophrenic patient including over protective families, controlling responses from medical and social services and feelings of powerlessness may provide the catalyst for the formation of persecutory beliefs. Research has shown that schizophrenic patients expressing persecutory delusions make external, stable and global attributions for negative events and excessively internal, stable and global attributions for positive events (Kaney and Bentall, 1989). This process might lead to either persecutory or grandiose type beliefs that may be seen as the result of the same cogntive bias. It is interesting that a separate sub syndrome of 'grandiosity' was uncovered in the present study not related to 'paranoid state' or 'delusions' (of other types). Thus, the process by which paranoid and grandiose behaviour/beliefs may occur in the present study

might be due to a cognitive biasing of information processing that occurs in trying to cope with extreme stress in one's personal environment. Of course, everyone has to cope with stress as part of everyday life, so why should the paranoid schizophrenic individual have to form and maintain such extreme ways of dealing with stress? The answer is probably two fold. Firstly, paranoid/grandiose behaviour can be seen as lying at the end of a long continuum of beliefs held by individuals or groups wishing to make sense out of their environments. An obvious example is of religious beliefs that provide much comfort and 'explanation' of personal circumstances for an individual. Secondly, it has been noted that schizophrenic individuals have particular difficulties in social inference or 'theory of mind' (Frith, 1992). A lack of 'theory of mind' is expressed by the inability to infer mental states in others, in terms of beliefs and intentions, and has been suggested as the basis of the social and communicative impairments seen in autistic individuals (Baron-Cohen et al., 1985). In this model, paranoid thinking and hallucinations of the third person are explained by a misinterpretation of others beliefs and intentions in a negative self-referential manner rather than lacking this ability completely (Kaney and Bentall.,1989). This type of impairment would suggest that the formation of paranoid delusional ideas and third person hallucinations result from poor social competence or cognition. Recent studies highlighting disproportionate episodic memory dysfunction in various groups of schizophrenic individuals (McKenna et al., 1990; Tamlyn et al., 1992) and the misuse of appropriate regularities of input on present functioning (Gray et al., 1991) would signify that such cognitive impairments would underpin the schizophrenic patient's inability to access and apply appropriate social knowledge to new situations. Whereas

deficit symptoms would signify that there has been a complete shut down of social cognition (or due to poor experience of social situations, the knowledge for competent social activity has not been laid down at all), the impairment resulting in paranoid behaviour would signify that only episodic material of a self-negating bias is retrieved or that only self-negating episodic information is laid down in the first place, due to negative experiences. This latter explanation would tie in with the Bentall (1994) model expressing paranoid behaviour as predominantly a cognitive bias that results from poor personal experiences and stressful social environment along with poor neuropsychological processes. The paranoid syndrome in the present study may fit in with such a model and explain that the formation of such a sub syndrome is due to more than a direct correlation relationship with poor episodic memory functioning but that the evident dysfunction within this area compared to normal functioning has a significant part to play in the formation and maintenance of such paranoid symptoms. The other neuropsychological impairments expressed in the acute sample would also figure in the formation of these types of symptoms as the poor executive functioning abilities characterised by disinhibition and semantic word fluency along with semantic memory impairments would indicate that the system responsible for the misinterpretation of social situations involves an impairment in the control of the close interaction between the episodic memory system and the laying down of social knowledge (autobiographical or otherwise) as 'facts' in the semantic system (Parkin, 1987). The impairment in executive functioning would also indicate a difficulty in using stored social knowledge appropriately in novel situations, where the ability to make inferences is imperative (see Shallice, 1988). The psychomotor difficulties of

these patients may implicate that sub cortical pathology might have a significant influence on cognitive ability, especially executive or frontal ability, that is evidently impaired in the present patient sample. This type of impairment has been suggested as underpinning the negative aspects of schizophrenia (Pantelis et al., 1992) and is possibly involved in the formation of a syndrome as 'poverty of affect'. Pantelis et al. (1992) suggested that bradyphrenia or cognitive slowing has much in common with the the characteristics of sub-cortical dementia, which is, in turn, charactersied by memory problems with information retrieval. As the memory impairments may be integral to the understanding of the syndromes in the present study, the robust psychomotor ability differences between the acute sample and controls might indicate the specific mechanism i.e. retrieval that characterises the memory impairment shown here.

In conclusion, the five emergent factors or sub syndrome sof acute schizophrenia were not related to neuropsychological functioning directly. The significant impairments in the areas of executive and particularly, memory and psychomotor functioning, might indicate which neuropsychological mechanisms underpin the cognitive biases, that result in impaired social cognition, that, in turn, more directly underpin the syndromes expressed at this stage of the illness. In comparison to studies of the sub syndromes of stable chronic patients, the acute stage appears to involve more disparate syndromes, highlighting a 'paranoid state' sub syndrome that fits into recent studies explaining such behaviour as an amalgam of personal, environmental and neuropsychological deficits. Future studies ought to take into account an

individuals relationship with their environment, especially in the investigation of symptom expression in first episode schizophrenia. Most first episodes of schizophrenia arise as a disease of early adulthood, and may be explained when levels of personal and environmental stress interact with fundamental neuropsychological impairments that results in bizarre beliefs and behaviours which protect the individual's self esteem, in terms of coping, but leaves a dependence on a behavioural system incompatible with healthy social relations.

CHAPTER 5: THE NEUROPSYCHOLOGY OF TREATMENT RESISTANT SCHIZOPHRENIA, MEDICATION AND SYMPTOMS.

5.1 INTRODUCTION

5.1.1 Neuroleptic Medication in the treatment of Schizophrenia

Antipsychotic medication has been available to clinicians for over 40 years. Due to their ameliorating effects on schizophrenic symptoms, in particular positive symptoms, these drugs have enabled many patients to resume relatively normal lives. Antipsychotic or neuroleptic medication is presently prescribed for both the treatment of acute exacerbations of schizophrenic symptoms and for the prevention of relapse in patients who have recovered from a psychotic episode (Marder et al., 1991). However, the process by which neuroleptics produce their beneficial effects is largely unknown (King, 1990). The mediation of typical neuroleptic activity has been proposed as an affinity for blocking dopamine, in particular D2, receptors (Petroutka and Snyder, 1980; Creese, 1983). In light of additional research demonstrating that dopamine agonists (i.e. amphetamines) can induce psychotic behaviour (Connell, 1958; Meltzer and Stahl, 1976), overactive dopamine neurotransmission has been favoured as an underlying explanation of schizophrenic symptomatology. In fact, studies have shown that dopamine antagonism is necessary in the amelioration of symptoms (Johnstone et al., 1978). However, there appears to be a delay between neuroleptic metabolism and clinical benefit, even though dopamine receptor blockade happens almost immediately (Cotes et al., 1978). Dopamine blockage may, therefore, play a role secondary to modulation in a more direct neurotransmission system or act in a combination of neurotransmissions ultimately responsible for a

reduction in schizophrenic symptomatology (Frith, 1992). This, as yet, has to be confirmed.

Neuroleptic medication, however, is far from curative and is limited in its activity. Not all schizophrenic patients derive beneficial effects from medication. Hogarty et al. (1974) estimates about 50% of patients relapse within two years despite medication. Davis et al. (1980) reported that up to 20% of patients derive very little or no benefit at all from typical neuroleptic medication.

A major limitation of standard antipsychotic drugs are thier proclivity to produce, often serious, extrapyramidal side-effects (EPS). In an epidemiological review, Ayd (1983) found 62% of his large sample (n=5000) to have neuroleptic-induced EPS. Intermediate EPS i.e occurring after weeks/months of medication, of the phenothiazine (e.g. chlorpromazine) and butyrophone (e.g. haloperidol) classes of antipsychotics include parkinsonian-type symptoms e.g. rigidity, tremor, akinesia (poor motor initiation) and bradykinesia (motor slowing) (Marsden et al., 1975). These types of symptoms have been suggested as occurring in approximately 40% of medicated patients (Enna and Coyle, 1983). An obvious problem of such side effects, as akinesia and bradykinesia, is their similarity to the deficit state symtoms of schizophrenia and their possible misinterpretation as clinical symptoms such as flattened affect (Mayer et al., 1985; Blanchard and Neale, 1992). However, these type of EPS can be reduced by either concomitant anticholinergic medication e.g. procyclidine, or by termination of medication. Akathisia, distressing subjective restlessness, can also occur after intermediate antipsychotic administration, but has a poorer response to adjunctive medication although beta-blockers may provide some respite (Black et al., 1985). A more serious form of EPS which occurs after protracted periods on antipsychotic medication i.e. months/years is tardive dyskinesia

which is characterised by abnormal involuntary movements, particularly of the mouth, perioral area, limbs and trunk (Black et al., 1985). This state may be irreversible and can get worse after drug withdrawal (Stahl and Wets, 1988)

Although, adjunctive medication is prescribed to counter the concomitant EPS of neuroleptics (i.e. anticholinergics e.g. procyclidine), researchers are looking at drugs beyond typical antipsychotics whose activity can potentially avoid disturbing and often permanent side effects. One of the, initially, most promising of these atypical drugs is clozapine. Clozapine is a dibenzodiazepine with a relatively weak affinity for D1 and D2 receptors but possesses significant blocking effects for serotonergic, alpha1 and histaminergic receptors, as well as possessing potent anticholinergic properties. Because of its anticholinergic properties and weak dopamine affinity, clozapine elicits few side effects associated with typical neuroleptics, including tardive dyskinesia (Juul Povlsen et al., 1985). Despite these encouraging observations, clozapine has been associated with other side effects, some life threatening. Deaths have been reported due to reduced white blood cell counts after clozapine administration (Griffith and Saameli, 1975). Despite such potentially harmful consequences, clinicians believe that clozapine, with close haematological monitoring, may have a beneficial role to play in the management of patients who are treatment refractory to typical medication (Kane et al., 1988; Marder et al, 1991). In a multicentre trial, Kane et al. (1988) found that schizophrenic patients, shown to be unresponsive to haloperidol, showed greater clinical improvement including negative as well as positive aspects of the disease with clozapine than with chlorpromazine (with adjunctive anticholinergic medication) administration (268 patients were randomised into separate treatment groups: 126 in the clozapine group, 142 in the chlorpromazine group). Although, no cases of agranulocytosis occurred, the authors

suggested that clozapine be restricted to treatment refractory groups of patients as the potentially fatal side effects of this drug cannot be ignored.

Another atypical neuroleptic of note, that has only recently been marketed in the U.K., is risperidone. This is a benzioxazole derivative possessing potent serotinergic (S2) and dopaminergic (D2) blocking properties, but none for cholinergic receptors (Janssen et al., 1988; Leysen et al., 1988). It has also been shown to provoke fewer EPS in animals (Megens et al., 1988) and in schizophrenic patients (Borison et al., 1992) than either typical antipsychotic medication i.e. haloperidol or placebo. Marder and Meibach (1994), in a multicentre trial in the U.S., looked at the efficacy of risperidone versus haloperidol versus placebo. One hundred and eighty three patients randomly assigned to specific treatment groups: placebo, 2mg, 6mg, 10mg or 16mg Risperidone or 20 mg haloperidol, completed a double blind study of eight weeks duration. Ratings of schizophrenic symptoms were recorded on the Positive and Negative Syndrome Scale (Kay et al., 1987). Positive symptoms were significantly lower in the 6mg, 10mg and 16mg of Risperidone and haloperidol groups than in the placebo condition. Negative symptoms were significantly reduced in the 6mg and 16mg conditions only compared to placebo. EPS were higher in the 16mg and haloperidol conditions than placebo-there was no difference with the 6mg dose. The study provided support for risperidone constituting a new potent antipsychotic which targets both positive and negative dimensions of schizophrenia more effectively than standard medication without EPS (at low to mid range doses). Similar to the role proffered for clozapine, risperidone may provide a potent tool in the drug therapy of treatment resistant patients more likely to be characterised by negative symptoms. Also, as the efficacy of risperidone indicates a possible role for the serotinergic system in the mediation of schizophrenic symptoms, further investigations may

provide a clearer pattern of the combinations and relative roles of neurotransmitter systems involved in symptom mediation (Kane, 1994).

5.1.2 Neuroleptic Medication Effects on Cognition in Schizophrenia

The changes in neurochemistry and possible clinical improvements, alluded to above, would suggest concomitant changes in neuropsychological performance (Blanchard and Neale, 1992). Research is, therefore, needed to create a '.. bridge between our understanding of biochemical pharmacology and the physiological mechanisms underlying abnormal cognitive processes and clinical symptoms' (King, 1990 p.799). Indeed, several reviews exist summarising the research to date of the effects of neuroleptics on cognitive functioning. Spohn and Strauss (1989) concluded that a certain 'normalisation' of disordered thinking and attention/information processing follows neuroleptic medication, although normalisation may be limited and not directly related to clinical improvement. Also, as clinical improvement may possibly be characterised by amelioration of primarily positive symptoms, some related psychological functions are probably more 'medication sensitive' than others. Spohn and Strauss's (1989) review consciously avoided an analysis of neuropsychological test performance in favour of more general symptom related psychological functions. In a review encompassing neuropsychological test performance and neuroleptic effects, Cassens et al. (1990) found that acute administration of neuroleptics may impair performance on some but not all tasks requiring vigilance and attention and some tasks requiring motor functioning. However, improved performance on tasks involving sustained attention and visuospatial problem solving skills appears to follow chronic administration, less so at high doses (Spohn and Strauss, 1989). Improved performance on nine out of twelve tests of cognitive functioning was found after chronic administration of haloperidol and fluperlapine (an atypical neuroleptic

resembling clozapine) despite impaired performance after single doses, fluperlapine also improved psychomotor ability after chronic administration (Saletu et al., 1986). Despite this dichotomy, other reviews have concluded that, despite improvement on some tasks involving attention, there are actually very few changes in neuropsychological test performance even after chronic continuous neuroleptic administration (Heaton and Crowley, 1981). Medalia et al. (1988) concluded that neuropsychological functions may be affected differentially by neuroleptic action. Memory and fine motor co-ordination impairment was related to anticholinergic effects and dopamine blockage respectively. There was also some suggestion that neuroleptics may compromise planning ability. However, tests of language, attention, intelligence gave equivocal results while no changes were found in performance on tests of visual-motor co-ordination e.g. trail making test and digit symbol substitution. In fact, no consistent evidence was found for improvement in any of the neuropsychological tests.

The use of differing experimental designs and methods may explain the variation in the reported effects of neuroleptics on cognition (King, 1990). More consistent evidence exists for the deleterious effects of commonly prescribed anticholinergic medication on cognition, in particular memory functioning (Frith, 1984). Anticholinergics such as procyclidine and benztropine are prescribed to counter EPS. Impaired verbal recall has been particularly implicated after anticholinergic administration (Tune et al., 1982; Strauss et al., 1990). In a comparison using matched recall and recognition tests, Calev (1984a) found that patients medicated with neuroleptics and anticholinergics performed more poorly on both tests than patients taking solely neuroleptics, and more poorly on recall than recognition. However, the same author was unable to replicate these results with a different patient sample (Calev, 1984b). Despite this, memory problems, again characterised

by impaired recall, have been reported research studies investigating the effects on cognition of neuroleptics with anticholinergic properties (Perlick et al., 1986). Other research indicates that the effect of neuroleptics on memory can be related to the potency of their individual anticholinergic properties. Eitan et al. (1992) found thioridazine and chlorpromazine to impair short term verbal memory, noticeable only after cumulative doses, while haloperidol and trifluoperazine improved the same memory function. These differential drug effects on memory reflect the respective anticholinergic properties of the individual drugs. It appears that anticholinergic medication and neuroleptics with potent anticholinergic properties have the proclivity to produce significant but selective memory impairments in groups of schizophrenic patients. A problem, however, exists in the investigation of anticholinergic effects on memory, as marked memory impairment has been recently implicated as characteristic of the illness itself in drug naive patients (Saykin et al., 1991; 1994).

The effects of neuroleptics on cognition, described above, involve drugs with similar pharmacological characteristics i.e. the affinity to block dopamine receptors. To date there are very few studies investigating the effects of the so-called atypical neuroleptics on cognition, especially concerning 'higher level' cognitive functioning, with groups of schizophrenic patients. Goldberg et al. (1993) compared a small sample of patients with schizophrenic symptoms on a range of neuropsychological tests while taking conventional neuroleptics and again after an average of 15 months on clozapine. They found that, although symptom scores declined by an average of 40%, performance on neuropsychological tests including the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Wechsler Memory Scale (WMS) subtests and the Wisconsin Card Sort Test (WCST) remained essentially unchanged. However, many of the test results from both sessions indicated impaired performance compared to normative data. Therefore, rather than regarding neuropsychological

dysfunction as unrelated or as an epiphenomenon to the signs and symptoms of illness, the authors believed their results provided evidence supporting neuropsychological deficits as '..enduring and fundamental manifestations of the illness that account for much of the chronic social and vocational disability [typical of schizophrenic patients]' p.46. Significantly impaired performance was recorded over time concerning visual reproduction memory, attesting to the possible potent anticholinergic properties of clozapine.

The effects of neuroleptics on cognition in groups of schizophrenic patients appears complex. Even considering drugs with similar pharmacological properties, neuroleptic effects seem to depend on dose, duration of medication, the differing anticholinergic properties and the specific neuropsychological domains under investigation. The fact that a small but significant proportion of patients who are treatment refractory may distort medication effects is also problematic in this type of study (Spohn and Strauss, 1989). An account of the degree and type of EPS exhibited by medicated schizophrenic patients is also necessary as they may have significant effects on neuropsychological test performance, especially those involving psychomotor ability, independent of direct medication effects (Waddington, 1987; Spohn and Strauss, 1989). Researchers should, therefore, take into account all of the above in the study of neuroleptic action on cognition for valid results.

As stated above, recent studies have attested to the clinical efficacy of the new antipsychotic risperidone over more conventional neuroleptics (Marder and Meibach, 1994) and to the fact that there appears to be fewer concomitant EPS (Claus et al., 1991). Its introduction into clinical practice has been heralded a milestone in the pharmacological treatment of schizophrenia, representing important progress in a field comprising only the second new antipsychotic drug marketed (in the U.S., at

least) since 1975 (Kane, 1994). Researchers have also been excited at risperidone potential to help treatment resistant patients whose only hope, until now, had been with, clinically limited, clozapine therapy (Edwards, 1994). However, no research, at time of writing, has been published comparing the neuropsychological sequelae of risperidone administration against other forms of medication. It is important to see to what degree cognitive and psychomotor abilities can be effected, with such a potent antipsychotic, compared to standard medication as compromising of these functions may well comprise side effects in themselves and have direct effects on clinical usage (Edwards, 1994). This present study has allowed the comparison of symptom expression as well as neuropsychological performance in a controlled study over time to assess the efficacy of risperidone both clinically and neuropsychologically with respect to standard medication regimes. To our knowledge this is the first time such a study has been carried out with this new antipsychotic.

5.1.3 Aims of the Present Study

The present study was undertaken to assess the effects of different neuroleptic drug regimes on neuropsychological functioning, in a controlled trial, over a specified period, with a significant sub population of schizophrenic patients characterised by historical treatment resistance. Such an investigation should help our understanding of how neuropsychological functioning varies with psychopathology and dose in a comparison of neuroleptics with known different pharmacological properties. The study was designed to compare the symptom and neuropsychological changes before and after intensive administration of typical and atypical neuroleptics with standard medication with a group of patients who remain severely ill despite previous standard medication. In turn, the results may clarify the neurobehavioural sites of drug action

and lead to improved knowledge about the psychopharmacological mechanisms of the respective neuroleptics (Bilder et al., 1992).

5.2 METHODS

The present study constituted a component to a larger study , carried out at the Royal Edinburgh Hospital in the University of Edinburgh Department of Psychiatry to compare risperidone and chlorpromazine in an intensive versus standard management programme of treatment resistant schizophrenia.

5.2.1 Study Design

5.2.1.1 Selection Criteria

The patients were selected from in and out patients at the Royal Edinburgh Hospital or from referrals from the East Lothian District. All patients had a contemporary DSMIII-R diagnosis of schizophrenia and conformed to the St Louis (Feighner et al., 1972) criteria for schizophrenia. All the patients demonstrated a degree of treatment resistance meeting the criteria of May et al. (1988) for level 4 (fair responders), level 5 (poor responders) or level 6 (severe treatment resistance) - see Appendix2 . Each patient gave written consent to their participation in the study that satisfied the requirements of the Lothian Health Board, Psychiatry/Clinical Psychology Ethics of Medical Research Sub-committee.

The patients were randomised into one of three different drug programmes

STUDY DESIGN OF MEDICATION CHANGES FOR HIGH CHLORPROMAZINE (HC), RISPERIDONE (R) AND COMPARISON/CONTROL GROUP (C)

DAY	GROUP		
	HC	**R**	**C**
0	Switch to CPZ equivalents. Use 5 mg Procyclidine BD	Same as 1.	Continue with all medication unchanged (unless required clinically) for the 63 day period.
7	Reduce CPZ from 100% to 50%. Reduce Procyclidine to 0.	Same as 1.	
14	Continue CPZ at 50%. No Procyclidine	Same as 1.	
21 to 35	Phased increase of CPZ from 50% to 150% (or maximum tolerated dose)	Switch to Risperidone 2mg BD to 8 mg BD (or optimum dose)	
35 to 63	Continue CPZ at 150% (or maximum tolerated dose	Continue Risperidone at 8mg BD (or optimum dose)	

CPZ = chlorpromazine.

All the groups received 9 weeks (63 days) active management. Groups HC and R were characterised by intensive management. After changing all medication for patients in groups HC and R to chlorpromazine equivalents, phased increased doses of chlorpromazine and risperidone respectively were administered up to 150% of baseline chlorpromazine levels or 16 mg of risperidone per day. If 150% doses were not clinically feasible maximum tolerated doses were administered. Group C patients continued on standard medication at the same dose (and injection frequency) together

with any anticholinergic needed for EPS for the 9 week period, changes were allowed according to the clinical interests of the individual patients. All drug and clinical management was carried out by trained nursing staff and senior psychiatrists.

5.2.2 Assessments

5.2.2.1 Neuropsychological Assessment

The neuropsychological test battery constructed for the present study was designed to encompass tests of neuropsychological functioning sensitive to the underlying cognitive abnormalities associated with schizophrenic symptomatology. In addition, the tests had to be presentable in parallel versions to assess functional change over time minimising practice effects associated with repeated testing.

5.2.2.2 Neuropsychological Test Battery

The neuropsychological tests were grouped by function. The tests were chosen to assess various dimensions of executive functioning, memory and psychomotor ability - (see Methods chapter for theoretical background and general description of the neuropsychological measures used in this study of the neuropsychology of schizophrenia).

Neuropsychological testing was carried out on four critical occasions. A baseline assessment was carried out on day 7, one week after the intensive management groups had been medicated on chlorpromazine equivalents of their pre study medication. Baseline was calculated on day 7 and not day 0 for two reasons. Firstly, the patients had to undergo many baseline ratings in terms of psychiatric and

haematological assessments so, in the interests of compliance, ethics and the desire to avoid 'assessment fatigue', baseline assessments were spread throughout the first week of the drug trial. No changes in dose were made during this period. Secondly, as the patients were taking drugs of various pharmacological groups during the pre study period, taking baseline at day 7 ensured that all the patients were taking the same medication but at their individual pre study doses, in chlorpromazine (cpz) equivalents.

Subsequent neuropsychological assessments were made at day 21 (at the end of one week at 50% of the baseline chlorpromazine dose), day 42 (at the end of one week on 150% of original dose of chlorpromazine for group HC, 16mg of risperidone for group R or, if less, the individual maximum tolerated dose of the respective drugs) and day 63 (after 3 weeks on 'maximum' doses). These days were chosen as critical points to allow the different doses to take effect (see table p.10).

5.2.2.3 Neuropsychological Measures (See Methods for details and justification)

a) **General intellectual functioning** was assessed at baseline only. Pre morbid intellectual functioning was assessed using the National Adult Reading Test (NART) (Nelson, 1982). Current intellectual functioning was measured using the Quick Test (Ammons and Ammons, 1962) and general cognitive functioning using the Mini Mental State Examination (MMSE) (Folstein et al., 1975; Dick et al, 1984).

b) The following measures of **executive functioning** were assessed on days 7, 21, 42 and 63 using parallel versions.

i) Verbal fluency was assessed by using the initial letters A, W, D and H (four high frequency letters were chosen from the Thorndike and Lodge (1944) index of

linguistic frequency for parallel testing and that 'easier' letters may be more discriminating in schizophrenia studies (Borkowski et al., 1967) and the semantic category animals. The initial letter and semantic category scores were totalled for each test session.

ii) The Intradimensional/Extradimensional Shift Test from the CANTAB, from the practice (day 7), parallel batteries 1 (day 21), 2 (day 42), 3 (day 63). This is a test of attention shifting ability and visual discrimination learning (Robbins et al., 1991). The number of completed sets was recorded along with the number of trials to reach criterion on stage 6 (an intradimensional shift) and stage 8 (an extradimensional shift). The proportion of patients per group passing or failing each stage of the test was also recorded to give an overall impression of group performance as not all patients were able to complete up to either stage 6 or 8.

The next set of executive functioning tests were administered on days 7 and 63 only due to the lack of parallel versions of the tests.

iii) The Stroop test (Trenerry et al., 1989) was administered to assess change in the ability to suppress a habitual response in favour of a novel one (Spreen and Strauss, 1991). A word-colour condition score was calculated to assess this test performance.

iv) A computerised version of the Continuous Performance Test (CPT) (Frith et al., 1991) was also administered to assess the ability to suppress inappropriate responses. The number of inappropriate responses was recorded.

v) The Tower of London Test from the CANTAB was administered to assess planning ability (Shallice and McCarthy, 1982; Robbins et al., 1991). The number of completed sets, average moves per set, initial and subsequent movement times per set and initial and subsequent 'pure' planning times per move per solution set

(experimental-motor control condition times) were recorded, after Owen et al. (1990).

c) **Memory functioning** was assessed using the following measures for days 7, 21, 42 and 63.

i) Working memory using digit span, forwards and backwards, was assessed by parallel versions included in the Randt Memory battery (Randt and Brown, 1983).

ii) Long term episodic memory functioning was measured using the four parallel versions of the Rivermead Behavioural Memory Test (RBMT; Wilson et al., 1985). Total profile scores were recorded.

iii) Parallel versions of computerised tests of short term non-verbal recognition memory were used from the CANTAB. Delayed matching to sample (DMTS), pattern and spatial recognition memory tests were administered. Total correct scores were recorded for pattern and spatial recognition tests and for simultaneous, 0sec, 4sec and 12sec delay conditions on the DMTS.

d) **Psychomotor ability** was assessed for all four time points.

i) Average motor and reaction latencies were recorded from stage 5 of the Reaction Time Task from the CANTAB using parallel versions.

ii) Visuo-spatial coding was assessed using the digit symbol substitution test (from the WAIS-R; Wechsler, 1981). Parallel versions were constructed using the original as a template by recoding the reference set. Total correct in 90s was recorded.

5.2.3 Psychiatric Ratings

Psychiatric ratings were taken on days 7 and 63 using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1989), covering 7 separate positive and

negative symptoms-see Methods for details. Individual positive and negative syndrome total scores were recorded. All ratings were made by a trained senior psychiatrist.

Signs of tardive dyskinesia were assessed by the Abnormal Involuntary Movement Scale (AIMS; US Department of Health, Education and Welfare, 1976). Parkinsonian-type extrapyramidal side effects (EPS) were assessed using the Targeting Abnormal Kinetic Effects (TAKE; Wojcik et al., 1980). Totals for both scales were recorded for days 7 and 63.

5.2.4 Subjects

Forty subjects in total, who fulfilled the entrance criteria, took part in, at least part, of the neuropsychological investigation. The patients were randomised into the three study groups as shown on table 3 (see Results). Eleven patients (8M, 3F) comprised the 'high chlorpromazine' group, fourteen patients (13M, 1F) comprised the 'risperidone' group and fifteen patients (9M, 6F) comprised the 'control/comparison' group. One male patient from the risperidone group withdrew after day 21. The patients were then medicated according to the study protocol as shown on tables 1 & 2.

5.2.5 Data Analysis

Demographic variables were analysed by multivariate anaysis of variance (MANOVA) for normally distributed data, by chi square for catagorical data. Symptom ratings, EPS ratings and neuropsychological performance variables were analysed using MANOVA with repeated measures for two (beginning and end) or

four (days 7, 21, 42 and 63) time points. Within group analyses were carried out using paired t-tests. All data analysis was carried out using SPSS 4.0 on a Macintosh Classic II personal computer.

5.2.5.1 Missing Data

It is important to note that missing data was practically unavoidable with such groups of severely ill patients. Missing data points for neuropsychological tests aswell as psychiatric ratings resulted from refusal or absence. A summary of the missing data points can be seen in the appendices. As MANOVA analysis requires full data sets for processing, it was necessary to account for the random missing data points that emerged during the study. Although the missing data points were few in number, to ignore them might have seriously omitted important data sets from final statistical analysis. To account for some of the missing data individual performance averages were substituted for the missing points for only one missing data point for groups HC and R (either day 21 or 42, never both) and only two missing data points for group C (i.e. day 21 and/or 42), otherwise the points remained void. No averages were used for day 7 or 63 assessments. This was thought to strike a balance between providing necessary scores for analysis and accounting for medication change in the intervention groups. This type of imputing reasonable data points, based on averages, can be legitimised by the fact that the data points computed were assumed to relate to trends in closely occurring time points, therefore, not confronting the problem of expected greater variance between time points seen with more protracted longitudinal data (Gibbons et al., 1993). However, such computational assumptions should be noted in the interpretation of final statistics. The missing data points are summarised in appendix .

TABLE 1

A SUMMARY OF TRIAL MEDICATION FOR HIGH CHLORPROMAZINE (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS (chlorpromazine (cpz) equivalents mg/day unless otherwise stated).

GROUP (n)		DAY 7	DAY 21	DAY42	DAY 63
HC(11)	Mean	496(314)	248(157)	743(472)	743(472)
	Range (median)	75-1000 (450)	37.5-500 (225)	112.5-1500 (675)	112.5-1500 (675)
R(14)	Mean	507(229)	250(112)	10(3.8)R*	10(4.0)R
	Range (median)	200-1000 (475)	100-500 (238)	4-16 (10)R	4-16 (10)R
C(15)	Mean	530(313)	469(267)	524(396)	524(396)
	Range (median)	100-1050 (470)	100-1050 (400)	100-1540 (400)	100-1540 (400)

R=RISPERIDONE

* 13 cases included as one patient withdrew after day 21.

TABLE 2

STUDY MEDICATION FOR HIGH CHLORPROMAZINE (HC), RISPERIDONE (R) AND CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS.

a) GROUP HC CPZ in mg per day unless stated. P=Procyclidine mgs per day.

PATIENT NO.	DAY7	DAY 21	DAY 42	DAY 63
004	1000 (10P)*	500**	1500	1500
008	200	100	300	300
014	500	250	750	750 (5P)
017	175	87.5	262.5	262.5
102	1000 (10P)	500 (5P)	1500	1500 (5P)
103	450	225	675	675
019	400 (10P)	200 (20P)	600	600
020	800 (10P)	400 (5P)	1200 (5P)	1200 (5P)
025	450	225	675	675
035	75	37.5	112.5	112.5
036	400	200	600	600

* (80mg Droperidol PRN) **(120mg Droperidol PRN) additional medication.

b) **GROUP R** (Doses in mg per day)

PATIENT NO.	DAY 7 CPZ	DAY 21 CPZ	DAY 42 RISPERIDONE	DAY 63 RISPERIDONE
001	750	375	16	16
007	450	225	8	8
010	500	250	12	12
016	600	300	WITHDREW	
105	200	100	8	10
018	700	350	8	8
106	350	175	6	6
022	350	175	12	12
023	700	300	16	16
108	1000 (10P)	500 (10P)	4	4
029	400	200	10	10
030	250	125 (10P)	10	10
033	600	300	14	14
034	250	124	6	4

c) GROUP C (Doses in CPZ equivalents mg per day). Medication for days 21, 42 and 63 same as baseline unless stated.

PATIENT NO.	DAY 7	DAY 21	DAY 42	DAY 63
005	400 (1P/2wks)			
006	266 (5P PRN)			
101	350 (10mg Tomazepam)	+20mg Tomazepam		
012	1050 (40P)			
013	640 (15P 10mg Diazepam)			
015	565 (5P)		965	
104	140 (5P in 12mths)			
021	1045 (15P)	545 (75mg Imipramine)		
107	745	635 (20mg Tomazepam)	Tomazepam reduced to 10mg	
024	924 (5P)		1540	
026	305			
027	470 (10P)			
032	700 (10P)	400 (10P)	200 (10P)	
039	250			
040	100			

5.3 RESULTS

5.3.1 Demographics (see table 3)

There was no overall group differences for sex ratio or age at the beginning of the drug trial. No significant overall group difference was observed when duration of psychiatric symptoms and number of hospitalisations were analysed. A significant overall group effect was demonstrated for time that the patients were judged to be functioning on level four or more of the May et al. criteria. Further analysis showed that, despite randomisation, the high chlorpromazine group to have spent significantly longer on this level of functioning or treatment resistance than either the risperidone

group (t=3.28 df(23) p<.01) or the control group (t=2.76 df(24) p<.05). No significant difference was seen between risperidone and control groups (t=-.13 df(27) p> .05). No overall significant group differences were observed in average cpz equivalent medication or numbers taking procyclidine over the year preceding the trial. Education background assessed by number of full time years spent in education was similar for all three groups. There was no overall difference in pre morbid intellectual functioning, as measured by NART performance, between the groups.

5.3.2 Symptom Ratings (see table 4)

Table 4 shows mean symptom totals grouped into positive and negative 'syndromes' for the three study groups for day 7 and day 63 of the trial. Positive symptom ratings did not show any group differences over time. Negative symptoms again could not differentiate between the groups over time; mean symptom ratings for each group remaining relatively constant over the nine weeks.

A within group analysis of positive and negative syndrome scores between days 7 and 63 showed no significant changes in total scores: for HC group, positive symptoms (t=2.06 df=10 p=.067), negative symptoms (t=-.37 df=10 p=.718); for R group, positive symptoms (t=-.86 df=12 p=.407), negative symptoms (t=-.06 df=12 p=.951); for C group, positive symptoms (t=1.32 df=14 p=.207), negative symptoms (t=.96 df=14 p=.355).

5.3.3 Extrapyramidal side effects (see table 5)

AIMS scores did not show any significant group effects over time. TAKE scores showed a group by time effect indicating that the groups significantly differed on this

measure of parkinsonian side effects from the beginning compared to the end of the study. However, further analysis showed that no group significantly differed from another at either day 7 or day 63, indicating that differences in scores were in differing directions and no one condition can be considered as superior than another in reducing scores over time. Inspection of the group means for days 7 and 63 would appear to confirm this. The results of the individual t-tests between groups were as follows:

HCvR; day 7 (t=1.69 df=23 p=.104), day 63 (t=-.48 df=21 p=.633).
HCvC; day 7 (t=1.40 df=24 p=.176), day 63 (t=-1.64 df=24 p=.115).
RvC; day 7 (t=-.65 df=27 p=.521), day 63 (t=-.76 df=25 p=.452).

5.3.4 General Intellectual Functioning (see table 6)

No overall significant group effects were observed, as assessed by the Quick IQ and the Mini Mental State Examination at day 7, although there was a trend toward significance on performance on the Quick IQ.

5.3.5 Executive Function Performance (see tables 7 to 16)

Performance on tests measuring various aspects of executive functioning for days 7, 21, 42 and 63 are reported on table 7:

a) On a measure of verbal fluency (initial letter+semantic category totals) no overall group difference was observed over time. However, each individual group appeared to significantly improve (by similar degrees) on their performance over time.

b) Performance on the ID/ED Set Shifting Test can be seen on tables 7 and 8. No overall group differences over time were observed when considering the mean totals of successfully completed sets of the task. No group differences were also observed over time for trials taken to reach criterion for both intradimensional and extradimensional shift stages. Table 8 shows the proportion of subjects per group passing and failing the intradimensional and extradimensional shift stages. The only significant group difference occurred on day 63 of the intradimensional set shift, with 45% of high cpz subjects passing this stage, compared with 91% and 86% of risperidone and control subjects.

Table 9 displays the group performances for the Stroop test and the Continuous Performance Test (CPT) for days 7 and 63. No overall significant group differences were recorded over time for the word-colour condition of the Stroop test or for number of inappropriate responses on the CPT.

Performance on the Tower of London test can be seen on tables 10 to 16. Table 10 refers to the study groups' total number of completed sets per level of task difficulty for days 7 and 63 of the drug trial. No significant group differences over time were observed for any of the solution sets. The number of average moves taken to complete each level of task difficulty for each group over time is shown on table 11. For two move solutions, a significant group by time effect was observed. Further analysis showed no significant differences between individual groups at either day 7 or 63. The individual between group analyses were as follows:

HCvR; day 7 (t=-1.62 df=21 p=.120), day 63 (t=.00 df=18 p=1.000)

HCvC; day 7 (t=.87 df=21 p=.393), day 63 (t=.36 df=22 p=.719)

RvC; day 7 (t=2.04 df=24 p=.052), day 63 (t=.36 df=22 p=.719)

No significant group by time effects were observed on average moves taken to complete either 3, 4 or 5 move solutions. However, all three groups improved significantly over time on their performance on the three move problems.

Table 12 shows the average times per group to complete the first move as part of the yoked motor control condition of the Tower of London test for days 7 and 63. No significant overall group by time differences were observed for 2, 3 or 4 move solution sets. The groups all improved significantly on their 3 move solution performance over time. Five move solution statistics were avoided as the high cpz group only possessed five valid cases for analysis which was deemed too few for the level of analysis required-as was the case for subsequent 5 move solution time analyses. Movement times subsequent to the first move over time are shown on table 13. Again, no overall group by time effects were observed but there was a significant overall improvement in the groups' performance on the 3 move problems between day 7 and 63.

Tables 14 and 15 refer to initiation and subsequent (to the first move) 'planning' times respectively for the Tower of London test for each trial group for days 7 and 63. Planning times correspond to times derived from subtracting yoked motor times from the experimental condition times. No significant group by time effects were observed at any level of task difficulty for either initiation or subsequent planning times per move. There was a significant time effect on subsequent planning times per move for three move solution problems. Table 16 shows an alternative analysis of the five move solution data. A significant group difference was observed considering the proportion of subjects reaching the five move solution problems on day 63 with only 64% of the

high cpz subjects attempting this type of problem compared to 100% of risperidone subjects and 87% of controls.

5.3.6 Memory Test Performance (see tables 17 & 18)

Table 17 shows the performances on the computerised memory tests from the CANTAB for all three study groups over the period of the drug trial. Table 17 a) to d) shows group performances on the delayed matching to sample task from the CANTAB for simultaneous, 0 sec, 4 sec and 12 sec delay conditions for days 7, 21, 42 and 63. No overall significant group differences were recorded over time for any of the delay conditions. However, for simultaneous and 12 sec delay conditions there was a significantly similar improvement in performance for all three study groups over the duration of the drug trial for these test conditions. Table 17 e) and f) shows group performance on the pattern and spatial recognition memory tests from the CANTAB for days 7, 21, 42 and 63. No overall significant group differences were observed on this test over time, although a significant improvement in performance of all the groups was recorded on the spatial memory test over the testing sessions.

Table 18 a) and b) shows group performances on digit span forwards and backwards for days 7, 21, 42 and 63. Again, no significant group by time differences were recorded. Performance on the digits forwards changed significantly to the same degree for all three groups over the duration of the trial. Table 18 c) displays mean total profile scores for all three groups on the Rivermead Behavioural Memory Test (RBMT) for days 7, 21, 42 and 63. No significant overall group difference over time was recorded.

5.3.7 Psychomotor Ability (see table 19)

Table 19 a) and b) shows the mean motor and reaction latencies from stage 5 of the Reaction Time task from the CANTAB for days 7, 21, 42 and 63 for all three study groups. No significant group differences over time were observed on either dimension of the reaction time measure. Table 19 c) shows group performances on the digit symbol substitution test over time. No significant group differences were observed over time, however, each individual group's performance appeared to improve significantly over time.

TABLE 3

DEMOGRAPHICS OF HIGH CPZ VERSUS RISPERIDONE VERSUS CONTROL GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS (MEANS AND SDS)

	HIGH CPZ	RISPERIDONE	CONTROL	F RATIO	SIG.
N	11	14	15		
M:F	8:3	13:1	9:6	LR=4.7	.1
AGE(yrs)	38.2(10.2)	41.7(11.7)	33.9(11.1)	1.79	.181
DURATION OF SYMPTOMS (yrs)	16.5(8.7)	18.4(12.5)	12.2(7.9)	1.47	.243
TIME AT LEVEL 4+(mths)	41.9(18.3)	21.7(12.5)	22.5(17.4)	6.04	.005
No. ADMINS	6.1(4.6)	7.8(7.4)	13.3(12.2)	2.38	.106
AV. CPZmg last year/day	493(273)	471(222)	593(465)	.51	.606
Numbers taking Proc.	1	2	2	LR=.18	.916
EDUC.(yrs)	12.1(2.9)	12.6(2.9)	11.2(1.2)	1.41	.257
NART	112.4(8.3)	105.2(11.5)	106.6(10.4)	1.60	.216

TABLE 4

POSITIVE AND NEGATIVE SYMPTOM RATINGS TOTALS AT DAYS 7 AND 63 FOR HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS (MEANS AND SDS)

	GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
POSITIVE SYMPTOMS						
	HC(11)	18.9 (7.7)	15.5 (7.5)	F=1.77	F=1.33	F=2.44
	R(13)	17.2 (5.9)	18.9 (6.7)	P=.184	P=.256	P=.102
	C(15)	22.1 (5.4)	20.6 (7.0)			
NEGATIVE SYMPTOMS						
	HC(11)	20.2 (5.1)	21.7 (16.4)	F=.23	F=.08	.62
	R(13)	19.5 (5.6)	19.6 (5.6)	P=.794	P=.779	.542
	C(15)	22.1 (5.4)	19.7 (4.6)			

TABLE 5

AIMS AND TAKE TOTALS FOR DAYS 7 AND 63 FOR HIGH CPZ (HC)VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS (MEANS AND SDS)

	GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
AIMS	HC(11)	6.9(8.8)	6.4(6.9)	F=.60	F=.83	F=1.59
	R(13)	6.0(6.5)	2.8(3.9)	P=.554	P=.369	P=.219
	C(15)	6.3(7.0)	7.2(7.6)			
TAKE	HC(11)	14.7(4.1)	12.2(3.9)	F=.18	F=.05	F=4.12
	R(12)	12.2(5.0)	13.2(5.6)	P=.838	P=.822	P=.025
	C(15)	12.5(4.1)	14.5(3.2)			

TABLE 6

CURRENT INTELLECTUAL FUNCTIONING OF HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS AT DAY 7 (BASELINE) (MEANS AND SDS)

	HC	R	C		F RATIO	SIG.
				MANOVA df (2,37)	1.50	.307
QUICK IQ	106.4 (17.0)	107.0 (18.4)	95.5 (15.3)		2.59	.089
MMSE	26.8 (5.1)	26.8 (3.1)	25.3 (4.0)		.647	.516

TABLE 7

EXECUTIVE FUNCTION PERFORMANCE OF HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS FOR DAYS 7, 21, 42 AND 63 (MEANS AND SDS).

A) VERBAL FLUENCY (TOTALS: INITIAL LETTER+SEMANTIC CATEGORY)

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	24.6 (6.9)	24.6 (7.9)	27.7 (8.6)	27.5 (7.9)	F=.19	F=8.36	F=.71
R(10)	23.2 (7.7)	25.4 (7.6)	27.2 (8.1)	25.8 (9.5)	P=.83	P=.000	P=.643
C(13)	20.6 (8.7)	24.6 (9.8)	26.5 (10.6)	24.8 (9.0)			

B) NUMBER OF COMPLETED SETS ON THE ID/ED SET SHIFTING TEST

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	5.6 (3.3)	6.3 (2.8)	6.6 (2.8)	4.7 (3.5)	F=1.31	F=2.38	F=.76
R(10)	6.7 (2.9)	7.0 (2.8)	7.4 (2.2)	7.3 (2.5)	P=.285	P=.089	P=.603
C(14)	7.0 (2.7)	7.0 (2.8)	7.5 (2.1)	7.3 (2.6)			

C) NUMBER OF TRIALS TO REACH CRITERION ON STAGE 6 THE INTRADIMENSIONAL SET SHIFT ON THE ID/ED SET SHIFTING TEST

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	24.6 (17.9)	25.5 (19.6)	18.8 (17.4)	34.4 (21.5)	F=2.26	F=1.54	F=1.23
R(10)	20.0 (18.8)	22.8 (23.1)	14.4 (13.4)	15.5 (15.8)	P=.122	P=.209	P=.298
C(13)	17.8 (18.5)	16.7 (15.5)	12.2 (12.8)	11.1 (11.9)			

D) NUMBER OF TRIALS TO REACH CRITERION ON STAGE 8 THE EXTRADIMENSIONAL SET SHIFT ON THE ID/ED SET SHIFTING TEST

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	38.6	38.1	38.5	39.5	F=.45	F=.06	F=.42
	(17.9)	(17.4)	(17.6)	(17.9)			
R(9)	34.6	33.1	32.9	35.9	P=.642	P=.98	F=.864
	(18.8)	(20.1)	(20.4)	(18.6)			
C(13)	31.8	33.2	36.4	29.6			
	(21.0)	(18.3)	(14.5)	(20.0)			

TABLE 8

PROPORTION OF SUBJECTS SUCESSFULLY COMPLETING (PASSING) AND FAILING STAGE 6-AN INTRADIMENSIONAL SHIFT AND STAGE 8-AN EXTRADIMENSIONAL SHIFT ON THE ID/ED SET SHIFTING TEST FOR DAYS 7, 21, 42, 63 FOR HIGH CPZ (HC) VERSUS RISPERIDONE (R) AND CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS.

A) INTRADIMENSIONAL SHIFT

DAY	GROUP (n)	PASS(%)	FAIL(%)	LIKELIHOOD RATIO (df)	PROB.
7	HC(11)	7(64)	4(36)	1.19 (2)	.552
	R(14)	9(64)	5(36)		
	C(15)	12(80)	3(20)		
21	HC(11)	9(82)	2(18)	.60 (2)	.741
	R(12)	9(75)	3(25)		
	C(15)	13(87)	2(13)		
42	HC(11)	9(82)	2(18)	.78 (2)	.678
	R(11)	10(91)	1(9)		
	C(13)	13(93)	1(7)		
63	HC(11)	5(45)	6(55)	7.14 (2)	.028
	R(11)	10(91)	1(9)		
	C(14)	12(86)	2(14)		

B) EXTRADIMENSIONAL SHIFT

DAY	GROUP (n)	PASS(%)	FAIL(%)	LIKELIHOOD RATIO (df)	PROB.
7	HC(11)	4(36)	7(64)	.78 (2)	.667
	R(14)	6(43)	8(57)		
	C(15)	8(53)	7(47)		
21	HC(11)	4(36)	7(64)	.81 (2)	.668
	R(12)	5(42)	7(58)		
	C(15)	8(53)	7(47)		
42	HC(11)	4(36)	7(64)	1.21 (2)	.547
	R(11)	5(45)	6(55)		
	C(14)	8(57)	6(43)		
63	HC(11)	3(27)	8(73)	1.44 (2)	.486
	R(11)	5(45)	6(55)		
	C(14)	7(50)	7(50)		

TABLE 9

EXECUTIVE FUNCTION PERFORMANCE FOR HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS FOR DAYS 7 AND 63 (MEANS AND SDS)

A) STROOP TEST WORD-COLOUR PERFORMANCE

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	26.2 (20.9)	25.1 (22.9)	F=1.23	F=1.29	F=.36
R(9)	34.3 (28.0)	31.1 (23.7)	P=.307	P=.265	P=.699
C(14)	45.3 (30.8)	37.6 (31.3)			

B) CONTINUOUS PERFORMANCE TEST INAPPROPRIATE RESPONSES

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	1.6 (2.0)	2.2 (2.0)	F=.16	F=.03	F=.71
R(11)	2.6 (3.7)	1.7 (2.5)	P=.852	P=.862	P=.499
C(13)	2.4 (2.7)	2.4 (3.1)			

TABLE 10

THE TOWER OF LONDON TEST NUMBER OF COMPLETED SETS PER DEGREE OF TASK DIFFICULTY FOR HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS (MEANS AND SDS) FOR DAY 7 AND DAY 63.

A) 2 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	1.8(.6)	1.8(.6)	F=.63	F=.74	F=.80
R(10)	2.0(0)	2.0(0)	P=.542	P=.396	P=.459
C(13)	1.7(.8)	1.8(.6)			

B) 3 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	1.8(.6)	1.8(.6)	F=.63	F=.74	F=.396
R(10)	2.0(0)	2.0(0)	P=.542	P=.396	P=.459
C(13)	1.7(.8)	1.8(.6)			

C) 4 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	3.6(1.2)	3.6(1.2)	F=.63	F=.74	F=.80
R(10)	4.0(0)	4.0(0)	P=.542	P=.396	P=.459
C(13)	3.4(1.5)	3.7(1.1)			

D) 5 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	3.2(1.3)	3.2(1.3)	F=1.09	F=1.16	F=.29
R(10)	3.7(.9)	4.0(0)	P=.348	P=.290	P=.750
C(13)	3.4(1.5)	3.7(1.1)			

TABLE 11

THE TOWER OF LONDON TEST AVERAGE MOVES TAKEN TO COMPLETE TASKS PER DEGREE OF TASK DIFFICULTY FOR HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS (MEANS AND SDS) FOR DAY 7 AND DAY 63.

A) 2 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	2.0(0)	2.0(0)	F=2.29	F=4.20	F=4.09
R(10)	2.4(.7)	2.0(0)	P=.119	P=.050	P=.027
C(12)	1.8(.6)	1.8(.6)			

B) 3 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	4.1(1.2)	3.7(.9)	F=1.82	F=8.41	F=.25
R(10)	4.2(1.3)	3.4(.6)	P=.181	P=.007	P=.783
C(12)	3.5(1.4)	2.9(1.0)			

C) 4 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	5.9(1.0)	6.2(1.1)	F=1.32	F=.46	F=.89
R(10)	6.4(.9)	5.8(1.1)	P=.282	P=.502	P=.424
C(12)	5.4(1.9)	5.3(1.8)			

D) 5 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	8.9(2.0)	8.6(2.3)	F=2.12	F=1.13	F=.75
R(10)	8.5(1.7)	8.6(1.4)	P=.139	P=.298	.482
C(12)	7.7(2.6)	6.8(2.4)			

TABLE 12

THE TOWER OF LONDON TEST MOTOR INITIATION TIMES FOR HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS (MEANS AND SDS in ms) FOR DAY 7 AND DAY 63.

A) 2 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	2132(739)	1889(647)	F=3.80	F=.71	F=.20
R(10)	3755(3936)	3108(2045)	P=.035	P=.407	P=.823
C(11)	1698(589)	1621(857)			

B) 3 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	2346(1034)	1439(332)	F=1.22	F=5.75	F=.57
R(10)	2567(2355)	2193(989)	P=.312	P=.023	P=.570
C(11)	1871(1122)	1489(509)			

C) 4 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	1975(566)	1984(683)	F=1.38	F=1.54	F=1.79
R(10)	2713(1845)	1939(605)	P=.268	P=.224	P=.186
C(11)	1714(730)	1745(916)			

D) 5 MOVE SOLUTIONS-GROUP 1 ONLY POSSESSED 5 VALID CASES-TOO FEW FOR THE ABOVE STATISTICS RATHER SEE TABLE

TABLE 13

THE TOWER OF LONDON TEST MOTOR TIMES SUBSEQUENT TO THE FIRST MOVE FOR HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS (MEANS AND SDS in ms) FOR DAY 7 AND DAY 63.

A) 2 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	1602(466)	1411(625)	F=3.97	F=2.24	F=.34
R(10)	1721(599)	1565(541)	P=.03	P=.146	P=.712
C(11)	1175(241)	1144(211)			

B) 3 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	2314(1292)	1598(396)	F=2.31	F=6.89	F=.84
R(10)	2113(831)	1917(635)	P=.118	P=.014	P=.443
C(11)	1720(553)	1341(186)			

C) 4 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	1987(433)	1807(382)	F=2.65	F=3.35	F=.01
R(10)	2354(808)	2182(790)	P=.088	P=.078	P=.991
C(11)	1890(566)	1685(240)			

D) 5 MOVE SOLUTIONS-GROUP 1 ONLY POSSESSED 5 VALID CASES-TOO FEW FOR THE ABOVE STATISTICS RATHER SEE TABLE

TABLE 14

THE TOWER OF LONDON TEST PLANNING INITIATION TIMES FOR HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS (MEANS AND SDS in ms) FOR DAY 7 AND DAY 63.

A) 2 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	1817(1569)	1491(1719)	F=.52	F=2.38	F=.18
R(10)	2692(2091)	1759(1390)	P=.600	P=.134	P=.839
C(11)	2410(2043)	1769(1500)			

B) 3 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	4213(3551)	3964(4320)	F=.19	F=1.16	F=.23
R(10)	5659(3999)	4266(4199)	P=.830	P=.291	P=.798
C(11)	4540(3178)	3930(4273)			

C) 4 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	4029(4486)	6139(6807)	F=.03	F=.10	F=1.42
R(10)	5436(2686)	5912(6599)	P=.969	P=.760	P=.258
C(11)	7432(12280)	3398(1820)			

D) 5 MOVE SOLUTIONS-GROUP 1 ONLY POSSESSED 5 VALID CASES-TOO FEW FOR THE ABOVE STATISTICS RATHER SEE TABLE

TABLE 15

THE TOWER OF LONDON TEST PLANNING TIMES PER MOVE SUBSEQUENT TO THE FIRST MOVE FOR HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS (MEANS AND SDS in ms) FOR DAY 7 AND DAY 63.

A) 2 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	587(757)	831(1982)	F=.47	F=.00	F=.21
R(10)	748(680)	700(1700)	P=.631	P=.994	P=.810
C(11)	516(449)	314(353)			

B) 3 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	1558(2652)	611(675)	F=1.84	F=7.24	F=.43
R(10)	3287(4055)	1209(1150)	P=.177	P=.012	P=.658
C(11)	1640(1778)	453(567)			

C) 4 MOVE SOLUTIONS

GROUP (n)	DAY 7	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	2909(1758)	3021(2767)	F=1.96	F=2.33	F=.78
R(10)	3706(3409)	2616(2153)	P=.160	P=.138	P=.470
C(11)	2339(1965)	1076(1055)			

D) 5 MOVE SOLUTIONS-GROUP 1 ONLY POSSESSED 5 VALID CASES-TOO FEW FOR THE ABOVE STATISTICS RATHER SEE TABLE

TABLE 16

THE TOWER OF LONDON TEST PROPORTION OF SUBJECTS COMPLETING ALL FIVE MOVE SOLUTIONS FOR HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS ON DAY 7 AND DAY 63.

	GROUP (n)			LIKELIHOOD RATIO (df)	PROB.
	HC(11)	R(14)	C(15)		
DAY 7	7(64%)	13(93%)	13(87%)	3.69 (2)	.158
DAY 63	7(64%)	14(100%)	13(87%)	7.62 (2)	.022

TABLE 17

MEMORY TEST PERFORMANCE OF HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS FOR DAYS 7, 21, 42 AND 63 (MEANS AND SDS).

A) DELAYED MATCHING TO SAMPLE (DMTS) SIMULTANEOUS DISPLAY

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	7.5 (3.0)	8.4 (2.5)	8.5 (2.0)	8.7 (1.8)	F=.71	F=4.65	F=.72
R(10)	9.0 (8.4)	8.8 (.9)	9.5 (.9)	9.5 (.7)	P=.498	P=.005	P=.634
C(14)	8.4 (2.1)	8.9 (1.5)	8.9 (2.4)	9.1 (2.4)			

B) DMTS 0 SEC DELAY

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	6.5(1.9)	6.8 (2.7)	6.9 (2.6)	7.4 (2.8)	F=.66	F=2.44	F=1.36
R(10)	7.6(1.0)	7.8 (1.3)	8.3 (1.1)	7.2 (1.7)	P=.524	P=.069	P=.239
C(14)	6.4(1.7)	6.9 (1.7)	7.4 (2.4)	7.4 (2.0)			

C) DMTS 4 SEC DELAY

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	6.0(1.9)	6.7 (1.8)	5.7 (2.3)	6.6 (2.5)	F=.25	F=.57	F=.64
R(10)	5.9(2.2)	6.8 (2.0)	7.2 (1.7)	6.9 (2.1)	P=.780	P=1.21	P=.306
C(14)	7.0(2.6)	6.3 (2.4)	6.6 (1.6)	6.9 (2.0)			

D) DMTS 12 SEC DELAY

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(10)	4.2(2.0)	5.7 (1.9)	6.1 (2.9)	5.2 (2.7)	F=.65	F=4.53	F=1.37
R(10)	5.0 (.8)	7.0 (2.7)	6.7 (1.8)	5.7 (2.4)	P=.531	P=.005	P=.233
C(14)	5.5(1.8)	5.9 (1.8)	5.2 (2.3)	5.4 (2.0)			

E) PATTERN RECOGNITION MEMORY TEST

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	16.4 (2.7)	17.0 (3.4)	17.5 (4.1)	17.7 (4.2)	F=.65	F=2.24	F=.26
R(10)	18.0 (3.5)	18.4 (4.3)	19.6 (3.5)	18.9 (2.9)	P=.531	P=.088	P=.955
C(14)	17.3 (2.9)	17.5 (3.7)	18.1 (4.3)	17.6 (4.3)			

F) SPATIAL RECOGNITION MEMORY TEST

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	12.9 (2.0)	12.4 (2.0)	11.4 (2.5)	12.1 (2.5)	F=.28	F=4.75	F=.27
R(10)	14.4 (2.8)	13.0 (3.6)	11.8 (3.4)	12.4 (2.7)	P=.760	P=.004	P=.951
C(14)	13.4 (3.6)	12.5 (2.3)	11.7 (3.1)	12.8 (3.5)			

TABLE 18

MEMORY TEST PERFORMANCE (CONT.) OF HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS FOR DAYS 7, 21, 42 AND 63 (MEANS AND SDS)

A) DIGIT SPAN FORWARDS

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	7.3(2.6)	8.1 (1.3)	7.7 (1.2)	7.3 (1.3)	F=.01	F=3.80	F=.38
R(10)	7.5(1.3)	7.7 (1.5)	7.6 (1.4)	7.4 (1.8)	P=.986	P=.02	P=.887
C(14)	7.4(1.3)	7.8 (1.1)	7.5 (1.6)	7.3 (1.7)			

B) DIGIT SPAN BACKWARDS

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	4.5(1.8)	4.1 (1.6)	4.5 (1.8)	4.6 (1.7)	F=.89	F=1.47	F=.72
R(10)	5.0(2.2)	5.4 (1.8)	5.5 (1.5)	5.5 (1.4)	P=.419	P=.227	P=.632
C(14)	4.4(1.8)	4.7 (1.9)	4.9 (1.8)	4.8 (1.7)			

C) RIVERMEAD BEHAVIOURAL MEMORY TEST PROFILE SCORE TOTALS

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(11)	17.0 (6.4)	18.6 (5.8)	17.0 (5.3)	17.8 (4.3)	F=.47	F=.81	F=.96
R(10)	18.6 (5.3)	19.2 (3.9)	18.8 (2.8)	19.3 (4.3)	P=.626	P=.498	P=.462
C(14)	16.7 (5.6)	16.9 (6.2)	17.6 (5.4)	16.9 (6.4)			

TABLE 19

PSYCHOMOTOR ABILITY TEST PERFORMANCE OF HIGH CPZ (HC) VERSUS RISPERIDONE (R) VERSUS CONTROL (C) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS FOR DAYS 7, 21, 42 AND 63 (MEANS AND SDS)

A) MOTOR LATENCY FROM REACTION TIME TEST LEVEL 5 (CANTAB) (ms)

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(9)	646 (327)	646 (299)	661 (312)	617 (226)	F=.07	F=1.64	F=1.52
R(10)	592 (148)	606 (113)	633 (135)	743 (188)	P=.937	P=.202	P=.190
C(14)	633 (198)	674 (226)	711 (251)	658 (183)			

B) REACTION LATENCY FROM REACTION TIME TEST LEVEL5 (CANTAB) (ms)

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(9)	427 (145)	403 (113)	421 (137)	431 (120)	F=.15	F=1.67	F=.69
R(10)	395 (109)	393 (101)	504 (422)	424 (138)	P=.857	P=.196	P=.658
C(14)	424 (125)	383 (63)	403 (91)	390 (960			

C) DIGIT SYMBOL SUBSTITUTION TEST PERFORMANCE

GROUP (n)	DAY 7	DAY 21	DAY 42	DAY 63	BETWEEN SUBJECTS	TIME	GROUP BY TIME
HC(9)	33.9 (12.1)	37.3 (13.5)	38.5 (13.5)	41.8 (12.0)	F=.01	F=3.12	F=.90
R(10)	35.8 (13.0)	35.7 (14.7)	38.4 (13.9)	37.9 (14.6)	P=.985	P=.040	P=.503
C(14)	35.8 (13.20	37.5 (10.7)	38.6 (12.1)	38.1 (14.7)			

5.4 DISCUSSION

The present study failed to show any discernible differences in neuropsychological functioning between groups of treatment resistant schizophrenic patients on differing drug regimes over time. There were no significant group differences in either positive or negative symptomatology when ratings were compared at the beginning and the end of the trial. Although an overall group by time effect was observed on parkinsonian-type (TAKE) scores, further analysis failed to show superior improvement of one regime over another. The AIMS also showed no group differences over time. Therefore, although previous research has pointed to the superior clinical efficacy of the atypical neuroleptic risperidone over standard treatments (Marder and Meibach, 1994), the current study suggests intensive use of this atypical neuroleptic possesses no clinical advantage over intensive use of chlorpromazine or standard neuroleptic therapies with groups of treatment resistant schizophrenic patients. The same response pattern applied for the analysis of extrapyramidal side effects associated with each regime.

Despite the lack of clinical evidence supporting one type of neuroleptic intervention over another, the study's major aim was to investigate if neuropsychological performance changed with drug type and dose over time and, if so, what relation performance had with clinical symptom ratings. In particular, the study aimed to investigate the neuropsychological effects of the new atypical neuroleptic, risperidone, and its relation to the neuropsychological effects of standard 'typical' drug regimes. In fact, no discernible group by time effects were observed on any of the various neuropsychological measures administered. Risperidone did not appear to possess any neuropsychological, as well as clinical, advantage (or disadvantage) over the standard regimes. Of the vast amount of performance data extracted from the

groups, during the trial, only performance on average moves taken to complete two move solutions on the Tower of London planning task showed a significant group by time effect. The two move solution problems were, however, the initial and easiest of the planning tasks. In fact, it appears that the Risperidone group was the only group to display poorer performance, over time, on this level of task difficulty, though not significantly. The more complex solution problems showed no significant group by time differences, although the groups, as a whole, showed poorer performances, over time, on the three move tasks. These problems, on face value at least, are probably more discriminating of planning ability than the easy but novel two move solutions. This being so, the high chlorpromazine group did show significantly fewer patients completing all the most difficult five move solutions. A group by time analysis of planning times for these solutions was unfeasible due to the small number of cases completing the five move solutions from the high chlorpromazine group. In addition, fewer of the members of the high chlorpromazine group succeeded on the intradimensional shift stage of the ID/ED set shifting task, compared to the other groups. Although these results might suggest that the high chlorpromazine patients found these particular executive tasks more difficult than the other groups, no overall significant discriminant executive impairment could be attributed to this group as, for the other executive tests, relative performances were similar.

The individual groups showed significant concurrent changes in performance over time on some of the neuropsychological tests. Performance on tests of verbal fluency, simultaneous and 12 sec delay conditions of a delayed matching to sample task, a spatial recognition memory task, a visuo-spatial coding task and digit span forwards test improved over time for all groups. All these tests used four parallel versions. It would seem that this improvement in performance indicated marked practice effects, ironically, on tests designed to avoid such confounders. However, as practice effects,

although controlled for as much as possible, might be an unavoidable fact of life, especially with testing time points so close together, a failure to show expected test-retest benefits after drug interventions has been suggested as implying an adverse effect of medication (Medalia et al., 1988). Practice effects, however, do remain a problem in the interpretation of drug effects on neuropsychological performance, involving repeated testing, despite the use of parallel versions. The tests showing possible practice effects, here, could be considered less demanding than other tests more 'cognitively complex' i.e. composed of multifunctional tasks e.g. ID/ED Set Shifting Test and Rivermead Behavioural Memory Test, which did not show improved performance over the four test sessions. Improved performance for the treatment refractory patients, as a whole, could be dependent on the degree of cognitive effort or combination of cognitive functions required to attempt a particular test.

In summary, it seems that neither intensive typical or atypical medication nor standard drug therapy gives clinical or neuropsychological function advantage over the other when administered to treatment resistant schizophrenic patients. This would imply that this type of patients' clinical symptoms do not vary according to dose and type of pharmacological action of the neuroleptics they are given. Performance on an array of neuropsychological tests mirrors this non differentiation of response. Research has, however, shown a selective clinical response, with this type of patient, in favour of the atypical neuroleptic clozapine over chlorpromazine after a six week trial (Kane et al., 1988). We might have expected a selective positive response for those patients on risperidone after the U.S. multicentre trial who found it significantly more clinically beneficial than haloperidol in a sub group of long term hospitalised patients (more than six months at the start of the trial), likely to have shown long term resistance to typical neuroleptics (Marder and Meibach, 1994). However, these results were

derived from a post hoc analysis of these patients clinical well being, thus this group was not so stringently classified (and randomised) as the present study's sample. The U.S. multitrial study also found that the *optimal* dose with the fewest EPS was 6mg of risperidone. In the present study, only *optimum* doses were analysed against each other. The mean optimum dose of risperidone in the present study was appreciably higher, 10mg, than in the multicentre trial. Thus, any future analyses of risperidone against typical neuroleptics with treatment resistant schizophrenic patients should address comparisons of clinical efficacy at lower doses than used in the present study. Unfortunately, the design of the study did not allow analysis of the patients on 6mg as the optimum dose for these patients was dictated clinically and ranged from 4 to 16 mg of risperidone.

As far as the analysis of the relationship between neuropsychological functioning and clinical profiles is concerned, Goldberg et al. (1993) demonstrated clinical improvement with clozapine without any variation in neuropsychological test performance. This would imply that certain cognitive deficits are relatively independent of clinical improvement in schizophrenia. This study, however, did not involve specifically treatment resistant patients. In the present study the relative stability of symptoms and neuropsychology, after three differing drug regimes, would suggest that, in our group(s), treatment resistance presents a relatively intractable state of affairs insensitive to drug manipulation including the novel atypical neuroleptic, risperidone, at high doses, demonstrating little effect on either symptom state or putative underlying neuropsychological dysfunction. It is of interest that, although no improvement was observed in the neuropsychological functioning of the groups relative to each other, the groups showed often poor neuropsychological functioning at baseline compared with published normative data e.g. Stroop and Rivermead scores. However, despite this, and, perhaps surprisingly for such a group

of long term treatment resistant patients, both pre morbid and current IQ levels fell within normal limits. These results do not necessarily mean that neuropsychological dysfunction comprises epiphenomena in the expression of schizophrenic symptoms with such a group of patients. It may signify that the certain areas of neuropsychological functioning are fundamental stubborn characteristics of treatment resistant schizophrenia and in tune, with Goldberg et al. (1993), might account for much of the enduring social and occupational disabilties seen with such patients.

The above observations were derived from small numbers of treatment resistant patients in each group. These small samples attest to the difficulty in recruiting and maintaining such severely ill patients in an intensive trial involving drug manipulation. Most of the patients screened for the trial, by definition, have had largely ambivalent experiences of several types of neuroleptics without any lasting clinical benefit. The use of small samples does affect the statistical power of the multivariate analyses used in the present study and thus the generalisation of the results. To clarify our results, additional analyses of individual cases, from each group, to check for individual changes in symptom and related neuropsychological performance, could be elicited from the wealth of data produced by such an intensive investigation. Despite this, it must be emphasised that the number of treatment resistant patients generated for the study was the product of two years recruitment by a senior psychiatrist who was employed specifically for this task. To date, we believe this study to be the largest of its kind with this problematic type of patient.

The presenting results also rely upon two fundamental assumptions. Firstly, as all the medication for the experimental groups was administered orally, we had to assume full compliance with taking the prescribed doses. Secondly, even if full compliance was in fact the case, we had to assume some universality of metabolism of the drugs

existed. The way to overcome such assumptions is to record neuroleptic serum levels of the patients at critical intervals, however, this facility was not available for the present study. This being so, the patients in the high chlorpromazine and risperidone groups were inpatients for at least 6 of the 9 weeks of the trial on a professorial research ward, designated for this type of research, with the accompanying close care and observation of trained clinical staff.

The present study was seen as an opportunity to compare neuropsychological performance between groups of severely ill schizophrenic patients taking optimum doses of neuroleptics with distinctly different biochemical activities. The neuropsychological test batteries were designed to assess a wide range of neuropsychological functions putatively sensitive to compromised behaviours in the expression of schizophrenic symptoms. The relative differing pharmacological activities and doses of the different drug regimes may have promised concomitant differentiation in symptom relief and neuropsychological performance. Dopamine antagonists have been thought to facilitate flexibility in response organisation i.e decreased redundancy or perseverative responding (Bilder et al., 1992). However, in the present study in a comparison of high doses of a strong dopamine antagonist (chlorpromazine) with a strong dopamine and strong serotonergic antagonist (risperidone) at high doses with largely low dose dopamine antagonists (control group) no differences were seen on tests reputed to be sensitive to executive 'organisational' functioning involving response flexibility i.e set shifting or Tower of London performance. Thus when comparing drugs with different pharmacological effects at differing doses, none discriminately changes the behavioural aspects of the treatment resistant patients over the other. Perhaps there is a biochemical response ceiling for this type of patient with these types of neuroleptics, limited in their action on stubborn and continuous dysfunctional symptoms and neuropsychological status.

It may be the case that these treatment resistant patients may be suffering the consequences of long term medication on the brain involving receptor regulation and cellular adaptation (Bilder et al., 1992). Thus, dependent on the degree of this effect, the potency of the drugs used in the present study at high doses may have decreased efficacy. This would be extremely difficult to adequately assess in any study of long term schizophrenia. Despite this, as stated above, even atypical neuroleptics, such as clozapine, that show significant symptom reduction in groups of treatment resistant patients may, nevertheless, fail to improve neuropsychological functioning (Kane et al., 1988; Goldberg et al., 1993).

Although, even with heterogeneous groups of schizophrenic patients neuroleptic drug effects on cognition have been seen as variable (King, 1990), for greater clarification, the results from the present study would require larger group studies with equally rigorously defined treatment resistant patients using wider, especially optimal, dose ranges and alternative types of neuroleptics preferably involving serum drug level records. Such studies may clarify the nature of treatment resistance in schizophrenia, its relation to neuropsychological functioning and symptom expression. It is of the utmost importance that treatments are found that may affect the fundamental functional deficits characteristic of a significant sub population of severely ill patients who remain relatively resistant to what is presently available in terms of neuroleptic medication. It may be the case that the therapeutic net needs to be widened to encompass tailored psychological and social aspects of functioning in concert with medication, which may have a useful maintenance role with these patients, to address the particular functional problems of presently treatment unresponsive schizophrenic patients.

CHAPTER 6: A NEUROPSYCHOLOGICAL STUDY OF GOOD VERSUS POOR OUTCOME SCHIZOPHRENIA

6.1 INTRODUCTION

It is increasingly recognised that schizophrenia is a heterogeneous condition with, as yet unidentified, causal factors and a variable outcome (Cooper, 1987). Although Kraepelin first conceived of dementia praecox as characterised largely by a progressive deterioration (Kraepelin, 1896), he later showed that some 13% of his 'dementia praecox' patients apparently reached full recovery (Kraepelin, 1919). Contemporary researchers and clinicians now realise there is a wide spectrum of response to the available treatment strategies for schizophrenia (e.g. May et al., 1988).

A substantial proportion of diagnosed schizophrenic patients experience some form of recovery, particularly since the advent of neuroleptic medication (especially the phenothiazines) in the early 1950s, and a possible change of public and professional attitudes towards caring for the mentally ill. In a review of 5 recent long term outcome studies, Harding et al. (1992) reported that at least half of each cohort had significantly improved or recovered when assessed at 20, 30 and 40 year follow up. Despite this, neuroleptic drug therapy, the major therapeutic tool in clinical practice, has been considered ineffectual with 10 to 30% of schizophrenic patients (Davis et al., 1980). In addition, other studies have shown that a significant sub group of initially responsive patients relapsed within two years of maintenance treatment (Kane & Lieberman, 1987). It is estimated that forty percent of initially drug responsive patients will suffer a relapse in the following year (Hogarty, 1984). Even despite relapse rates, at any given time, only 15-40% of non-relapsed schizophrenic patients are employed (Mosher and Feinsilver, 1973). In addition, with patients who

have been through psychosocial rehabilitation programmes, there is twice the expected relapse rate during the second year of follow-up (Hogarty, 1988), indicating that present forms of rehabilitation may play a delaying rather than a preventative role.

Given that this heterogeneous pattern of treatment response has been established, from a clinical and public health viewpoint it would be of great practical benefit to determine exactly which factors (whether clinical, pathophysiological, psychological or social) characterise the course and outcome of schizophrenia. In keeping with previous work suggesting differing typologies of schizophrenia, based on varying pathophysiology and/or treatment response (Crow, 1980), differentiating subtype by outcome may well enable the targeting of more homogeneous illness groups for suitable treatment regimes. In recent years researchers have constructed scales to aid the pursuit of typing by outcome along various functional dimensions (e.g. clinical, social, occupational etc.). For instance, May et al. (1988) have proposed a systematic approach encompassing 6 levels of treatment response which includes symptom amelioration and social/occupational status) (see Appendix 1). This has enabled the differentiation of heterogeneous groups of schizophrenic patients according to outcome, useful in the study of what factors predict or characterise treatment response.

6.1.1 Factors predicting outcome

In a recent, comprehensive, review Lieberman and Sobel (1993) listed the most consistent and robust correlates (predictors) of outcome in schizophrenia;

a) Pre morbid social adjustment

b) Pre morbid level of functioning

c) Mode of illness onset

d) Age of illness onset

e) Duration of illness

f) Duration of symptoms prior to first treatment

g) Negative symptoms of the defect state

When considering acute response to treatment, Lieberman et al (1992) found that pre morbid levels of functioning, younger age of illness onset and duration of illness were predictors of poor outcome (time to and level of remission). Lobel et al (1992) also stated that poor outcome was characterised by the duration of psychotic symptoms prior to treatment. Primary negative symptoms that persisted after psychotic symptom remission were also predictive of poor outcome. McEvoy et al (1992) also revealed that the shorter the period between onset of symptoms and initiation of treatment, the better the outcome.

With regard to long term outcome, early onset (<19yrs) and long duration of illness (>6 months) prior to admission correlate with poor outcome over 5, 10 and 15 year follow ups, from a sample of 330 first admission schizophrenic patients (Tsoi and Wong, 1991). Leff et al (1992), in the five year follow up of the International Pilot Study of Schizophrenia, found that both clinical and social outcome was better in 'developing' countries than in the industrialised world (perhaps due to cultural attitudes and increased social and vocational pressures/expectations of the 'industrialised individual'). Good outcome was characterised by abrupt onset of illness and female gender, whereas poor outcome was significantly associated with poor pre morbid social adjustment. The social status of the schizophrenic individual was also highlighted by Tien and Eaton (1992) who found that lower pre morbid

employment, social and education status were predictive risk factors for schizophrenia. Schmid et al (1991) in a 22.4 year follow up of 502 schizophrenic patients found that pre morbid status dominated all other measures accounting for outcome variance.

6.1.2 Psychological functioning and outcome in schizophrenia

In addition to outcome assessments along clinical and social functioning scales, researchers have also investigated the relation of various psychological aspects of functioning to outcome. Johnstone et al. (1990) used the Psychological Impairments Ratings Scale (Jablensky et al. 1980) in an investigation of functioning such as psychological tempo/slowness, initiative, social skills and personality factors, in relation to outcome status, defined by occupational status and number of inpatient days spent in hospital. Only lack of 'special assets', (including intelligence(weakly) and physical presentation were associated with poor occupational status, 'social charm' was relatively intact. Neither of these psychological functions was related to outcome in terms of hospital duration.

6.1.3 Neuropsychological functioning and Schizophrenia

Originally, Kraepelin (1919) and later Bleuler (1950) believed intellectual functioning to be left relatively intact in dementia praecox or the schizophrenias. However, recent studies have revealed significant intellectual impairment as a product of course (the 'dementia' of 'dementia praecox') (Johnstone et al, 1978; Nelson et al., 1990; Frith et al., 1991). Studies have shown gross neuropsychological impairments in group (Kolb and Wishaw, 1983) and single case study reports (Shallice et al., 1991). The vast majority of group studies, however, have tended to compare heterogeneous groups of

schizophrenic patients with either control or other psychiatric groups (e.g. Morice et al., 1990). The establishment of heterogeneous outcome now warrants research into how groups of different outcome function neuropsychologically.

It has been observed that neuropsychological deficits may be of significance in contributing to functional deficits in the areas of social and occupational activities (Jaeger et al. 1992). In terms of outcome studies some researchers have found neuropsychological test performance to be a valid predictor of treatment response, in terms of social and vocational disability (Marder et al. 1984). Kolalowska et al. (1985) found that poor outcome schizophrenic patients displayed significantly poorer performance on verbal memory ability, conceptual ability and spatial ability compared to good outcome patients. These cognitive deficits were related to severity of symptoms, social deterioration and resistance to treatment. Vocational outcome on follow up has been significantly associated with Wisconsin Card Sort Test performance on discharge (Jaeger and Douglas, 1992). Despite this, there is still no agreed pattern of relationships between neuropsychological performance and the other functional deficits observed in schizophrenia (Jaeger et al. 1992). If a pattern could be established, neuropsychological test performance may provide invaluable information that could be, potentially, prescriptive for specialised neurorehabilitation programmes.

This study will test the hypothesis that neuropsychological impairment will be associated with poor psychosocial outcome in schizophrenia.

6.1.4 Aims of the present study

1) To characterise the neuropsychological differences between a group of treatment responsive (good outcome) and treatment resistant (poor outcome) schizophrenic patients, using a variety of measures sensitive to various aspects of cognitive functioning putatively impaired in schizophrenia. To determine which neuropsychological functions best characterise poor outcome (i.e. executive, memory, psychomotor ability, lateralisation)

2) To assess the influence of various demographic and medication variables on the performance of the two responder groups.

6.2 METHOD

6.2.1 Subjects

Patients were recruited from in-, day- and out-patient populations at the Royal Edinburgh Hospital and associated hospitals. Patients were diagnosed as having schizophrenia in accordance with DSM-IIIR criteria (American Psychiatric Association, 1987). Their notes were examined for details of personal, family, social and psychiatric history: details which were recorded on a revised version of the DHSS Survey form (MacMillan et al, 1986). Patients were interviewed using the structured interview Present State Examination (PSE: Wing et al., 1974).

Patients had their outcome determined as treatment-responsive (good outcome) or treatment-resistant (poor outcome), according to the descriptive clinical criteria of May et al. (1988). Treatment responsiveness was limited to level 2; resistance- level 5 (see Appendix 1) (patients falling into treatment responsiveness level 1 were not included as response within one week of developing symptoms is not indicative of schizophrenia; patients in treatment response level 6 were not included due to the demands of the drug intake (haematological) analysis required). Presenting symptoms were assessed using the Manchester Symptoms Scale (Krawiecka et al., 1977). Outcome in social terms was assessed using Cooper's Scale (1961) and McGlashan's Cross-Sectional Outcome Scale (1984). All the psychiatric ratings were completed by a trained senior scientist.

The May et al. (1988) classification yielded two groups of 20 patients each, either treatment responsive or treatment resistant, who were then individually matched for age, sex and length of time since first episode.

The patients were also assessed for their personal medication history particularly for their exposure to anticholinergic drugs that might effect neuropsychological performance, especially in terms of memory performance (Frith, 1984).

6.2.3 Neuropsychological Assessment

For full details of the neuropsychological test battery see main Methods chapter.

a) **General intellectual functioning** was assessed by National Adult Reading Test (NART; Nelson, 1982) for pre morbid levels; Current intellectual level was assessed using the Quick IQ measure (Ammons and Ammons, 1962) and general cognitive functioning by the Mini Mental State Examination (Folstein et al., 1975; Dick et al, 1984). Paternal occupation (measured by The Standard Occupation Classifications; OPCS, 1991) was also used as a crude measure of socio-economic background to indicate pre morbid social advantage on account of possible problems associated with the interpretation of NART scores with groups of long term hospitalised patients (Crawford et al., 1992).

b) **Executive functioning** was assessed using the following measures: Verbal fluency (Animals and letter 'A'- 60 secs each), Stroop test (Trenerry et al., 1989), Trail Making Task A&B (Reitan, 1958), a computerised version of the Continuous Performance Test-CPT (Frith et al, 1991), the intradimensional/extradimensional set shift test (from CANTAB; Robbins et al., 1991); Tower of London test (from CANTAB).

c) **Memory functioning** was assessed using the following measures: short term working memory was assessed using the digit span test (forwards and backwards) (RANDT memory battery version A; Randt and Brown, 1983). Non verbal recognition memory was assessed using the Pattern recognition test, Spatial recognition test, Delayed matching to sample test (all from CANTAB). Long term

episodic memory was assessed using the Rivermead Behavioural Memory Test (RBMT; Wilson et al., 1985).

d) **Lateralisation** indices were calculated using Letter cancellation test; Star cancellation test; Line bisection test; Handedness scale (Wilson et al., 1987).

e) **Psychomotor ability** was assed using the Reaction time task (from CANTAB) and Digit symbol substitution test (WAIS-R, Wechsler, 1981).

f) **Attention and Co-operation was** assessed on a 5 point scale following Shakow (1981). These were not standardised scales but subjective indices of subject behaviour, by the examiner, at the time of testing.

6.2.4 Analysis of results

The results were analysed on a Macintosh Classic II computer using SPSS version 4.0. Demographic and medication variables were analysed by t-test and chi squared statistics dependent on the nature of the data set. Because the exercise was, in essence, exploratory, multiple comparisons were made, therefore, across the two groups using MANOVA. After initial analysis education, in terms of full time years of education, was entered as a covariate in further analysis of neuropsychological performance as the good outcome patients had experienced significantly more full time years of education than the poor outcome patients

Neuropsychological variables with incomplete data sets which were not included in the MANOVA, as they were few in number, were additionally analysed by independent t-tests.

Exposure to neuroleptics/anticholinergics and status at time of testing was analysed by chi squared statistics. Duration of medication status and levels of medication at time of testing were analysed by t-tests. Paternal occupation was analysed by a chi squared test. Pearson's correlations were used to test the association between education and neuropsychological performance. Neuropsychological variables, were also correlated (Pearsons) with anticholinergic status and hospital duration. Spearmans correlations were used to assess the relations between neuropsychological performance and clinical and other functional measures as these scales can not be assumed to be normally distributed.

6.2.5 Procedure

The above tests were administered on the day of the clinical interview (+/-1). The full battery took approximately 2 hours to complete, including appropriate rest periods suited to the individual testee.

Because of the nature of the patients under investigation i.e.. some being extremely ill, data loss during the relatively demanding investigation procedure was unavoidable.

Sometimes it was impossible to carry out a full neuropsychological examination at one sitting (e.g.. because of patient fatigue, , irritability). Therefore, due to some patients not attending follow up appointments some data sets were left incomplete. Analyses were based, therefore, on varying data sets per group.

6.2.6 Missing data sets

One good outcome patient (female) refused to complete any of the neuropsychological tests. One (male) good outcome group did not complete the Stroop test. Another (male) in the same group did not complete Trails A & B, the Mini Mental State Examination, all the lateralisation tests and the Stroop test.

As one would expect there was more missing data from the poor outcome group. One (male) did not complete digit symbol substitution, Trails A & B, Stroop, the Continuous Performance Test and all the CANTAB measures. Another (male) refused to complete the reaction time measure on CANTAB. One (female) missed the Trails A & B, The Mini Mental State Examination, the lateralisation tests and the Stroop test. However, the actual proportion of missing data that the above represented was surprisingly small, considering the type of patients and the size of the neuropsychological battery used. No major compensation for the missing data was thought necessary as group effects would not be grossly effected by providing averages etc., to provide for, at worst, the one or two missing data points.

6. 3 RESULTS

6.3.1 Demographic and Clinical details (see table 1)

The two groups of good and poor outcome patients were well matched for sample size and gender ratio. The groups were also well matched for age and average duration of their illnesses. The two groups differed significantly with regard to education background, as good outcome patients had experienced significantly more years of full time education than members of the poor outcome group. The groups did not differ in terms of socio-economic background as assessed by paternal occupations.

Unsurprisingly, the poor outcome patients had experienced significantly more psychiatric admissions and had endured longer periods in hospital than the good outcome patients. Members of the poor outcome group were taking, on average, significantly greater doses of neuroleptics (chlorpromazine (CPZ) equivalents) than the good outcome patients at time of testing. Both outcome groups were taking equivalent doses, on average, of anticholinergic medication at time of testing. Good outcome patients had experienced significantly shorter periods on anticholinergic medication than the poor outcome patients.

A brief comparison of the clinical symptom profiles using Manchester symptom scale totals showed a highly significant between group difference: the good outcome

patients showing less severe symptomatology than the poor outcome patients. On further analysis of the individual symptoms of the Manchester scale, only the ratings for coherently expressed delusions ($P<.0001$), hallucinations ($P<.0001$) and psychomotor retardation ($P<.05$) showed any significant outcome group differences

6.3.2 Neuropsychological test performance

6.3.2.1 General intellectual functioning (see table 2)

There was a highly significant difference between good and poor outcome groups pre morbid (NART) and current IQ (Quick IQ) scores. There was a decline in both groups intellectual performance from pre morbid to present states. The degree of the decline, however, was similar in both groups (t=-1.33 P=.192). On a measure of global cognitive ability (MMSE) the good outcome patients (X(sd): 28.3 (1.8)) scored significantly better than the poor outcome patients (X(sd): 25.2 (3.7)) (t=3.16 P<.005).

6.3.2.2 Executive functioning (see tables 3 to 15)

Overall group performances indicated that a significant between group difference occurred across the measures. Univariate analyses revealed that on the Continuous Performance Test, no group differences emerged when comparing omission scores. However, the poor outcome patients made significantly more commissions (inappropriate responses) than the good outcome patients. A highly significant difference in performance was recorded when Stroop (control minus experimental conditions) scores were compared in favour of the good outcome patients. Performance on a timed measure of attention switching, after controlling for simple

psychomotor speed [TRAILS (B-A)] showed no significant group differences. On a timed (category dependent) word fluency test no significant group differences were observed when the subjects produced words beginning with the letter 'A'. However, when the category changed to 'types of animals' the good outcome patients produced significantly more words than the poor outcome patients.

Set shifting ability was compared across the groups using the CANTAB ID/ED set shifting task. Tble 4 shows the proportions of patients from each outcome group successfully reaching criterion on each stage of the ID/ED set shifting task. No significant between group differences were recorded when the proportions of each group reaching criterion were compared at any of the 9 stages.

Table 5 shows trials taken to reach criterion at each stage for those patients who successfully reached stage 9 (last stage) of the task (11 'good' and 10 'poor'). No overall significant between group differences were observed. Table 6 shows group comparisons of trials to reach criterion for all patients completing each stage. No significant between group differences were observed at any stage.

Table 7 shows the number of errors made in reaching criterion at each stage for those patients successfully reaching stage 9. No overall significant between group difference was recorded. Table 8 compares all available error score data, from each group, for those patients successfully reaching criterion at each stage of the task. Only when

comparing error scores on stage 1 does any significant between group difference emerge, in favour of the good outcome group.

Planning ability was assessed by performance on the Tower of London test (see tables 9 to 15). All the patients (both good and poor outcome) were able to complete all the 2 and 3 move solution tests. All the good outcome patients were able to complete the 4 move solutions, 18 completed all the 5 move solutions, one good outcome patient was unable to complete any of these. 17 poor outcome patients were able to complete all 4 move solutions-one was unable to complete any. Fifteen poor outcome patients completed all the 5 move solutions. One poor outcome patient completed three 5 move solutions, one patient could complete only two of these problems and one was unable to complete any. Both groups completed roughly the same number of solution sets at each level of task difficulty.

No significant overall group differences emerged when average moves taken to complete each set were compared (table 10). This observation was based on those patients per group who had completed at least one 5 move solution successfully. Univariate analyses revealed a significant group difference when average scores taken to complete solution set 5 were compared. Table 11 refers to the proportion of patients per group who were able to complete solution sets in the minimum number of moves possible. No significant between group differences were observed although it is of note that the majority of the patients (of either group) could not complete the 4 or 5 move problems with minimum moves.

Table 12 displays the motor latencies for the yoked motor control condition of the Tower of London test. No significant overall differences emerged when comparing initiation and execution ('pick up' and 'place') times for each group at each level of task difficulty. Tables 13 and 14 show the initial and subsequent (to the first move) 'pure' planning times for each level of task difficulty. No significant group differences were observed.

6.3.2.3 Memory test performance (see tables 15 & 16)

Multivariate analysis of variance revealed an overall significant between group difference in memory functioning. On a delayed matching to sample task good outcome patients displayed better performance at 0 sec delay condition. Recognition (matching) scores were not significantly different at simultaneous, 4, or 12 sec delay conditions. Pattern recognition memory performance did not differ significantly between the groups. Spatial recognition memory performance did show a significant group difference in performance in favour of the good outcome group.

Short term auditory working memory, as assessed by a digit span measure, showed a significant group difference solely on digits backward, again in favour of the good outcome patients.

Performance on the Rivermead Behavioural Memory Test (profile score) revealed a highly significant between group difference. Good outcome patients displayed markedly superior scores on this test of long term episodic memory functioning. Table 15 shows multivariate analysis of the of the Rivermead raw scores for each subtest. Highly significant univariate differences were seen on the story recall (immediate and delayed recall) and to a lesser degree on remembering a message (immediate and delayed), orientation and remembering to ask a question on cue. It is interesting to note that no group differences were observed on the recognition tasks.

6.3.2.4 Performance on tests of neglect and lateralisation (see table 17)

No overall significant between group differences were observed on any of the measures of hemispatial neglect. Handedness was also recorded. the proportion of right handed patients was roughly equal in both groups (LR=.617 P=.432).

6.3.2.5 Psychomotor ability (see table 18)

Although no overall between group differences were observed, the resulting analysis showed a trend towards significance (P=.053). No univariate differences were recorded on a computerised reaction time task in terms of movement or reaction latencies. A highly significant difference, however, was observed when age scaled performances on the digit symbol substitution task were compared, in favour of the good outcome patients.

6.3.2.6 Examiner ratings of attention/concentration (see table 19)

Table 19 refers to the examiner's subjective appraisal of the patients' attention and cooperation throughout the test period. Good outcome patients were subjectively assessed as attending to the test situation and cooperating with the task demands significantly better than the poor outcome patients during testing.

6.3.2.7 Neuropsychological test performance and education (see tables 20 to 24)

As the educational backgrounds of the two outcome groups differed significantly (see table 1) and as the years of full time education correlated significantly with many of the test performances (Table 20), education was entered as a covariate and all the between group analyses of the neuropsychological variables were repeated (see tables 21 to 23). The many Tower of London variables were not entered as no significant differences were detected on initial analysis. The same reason applied to the omittance of lateralisation performance from this analysis.

No overall or univariate significant between group differences in executive functioning performance after controlling for education (table 21).

After controlling for education with the memory test performances, no overall significant between groups differences were recorded (table 22). On inspection of the univariate analyses, only Rivermead profile performance significantly discriminated between the groups still at a high level of significance ($P<.005$).

No significant group differences, in terms of psychomotor ability, between outcome groups was observed after controlling for education (table 23).

After controlling for education, there still emerged a significant between group difference concerning attention/cooperation during testing, in favour of the good outcome patients, but at a reduced level of significance (table 24) .

6.3.2.8 Rivermead Behavioural Memory Test and current intellectual functioning

The Rivermead Profile performance (RPT) correlated at a high level of significance with both present state IQ (Quick IQ) ($r=.7089$, $P<.01$) and Mini Mental State Examination ($r=.5778$, $P<.01$). Both these variables were then entered as covariates with the RPT scores. After controlling for present IQ, the RPT scores still differentiated between the two outcome groups (in favour of the good outcome patients) still at an elevated level of significance ($F=9.47$, $P<.005$). The significant between group difference also remained after controlling for global cognitive ability (MMSE results) ($F=8.45$, $P<.007$).

6.3.2.9 Medication and neuropsychological test performance

It has been suggested that memory can be affected by medication status, especially relating to anticholinergic intake (Frith, 1984). Therefore, the effects of anticholinergic medication were analysed with respect to the Rivermead scores. There was no significant difference between the numbers in each group who had ever experienced anticholinergic medication (LR=3.38 CHISQ=.659). As the levels of

anticholinergics at testing were similar in each group (see table 1) no correlations were performed with this variable. However, as the groups differed in duration of anticholinergic exposure (table 1), duration was correlated with RPT scores. The resulting correlation was statistically insignificant (r=-.006). Poor outcome patients were receiving higher doses of neuroleptics at the time of assessment and, therefore, chlorpromazine (CPZ) equivalents were correlated with RBMT performance (r=-.036 P<.05). RBMT scores were, therefore, reanalysed using CPZ dose equivalents as a covariate, the between group differences remained highly significant (F=11.8 P=.002). When duration of psychiatric admissions was considered, RBMT scores correlated significantly (r==.443 P<.01) indicating that poor RBMT performance was associated with long inpatient duration.

6.3.2.10 Analyses of the relationships between measures showing outcome group differences and education and the functional and symptom scales used as outcome measures (see tables 25 to 28)

Spearman's correlations were used to analyse these relationships as the functional (Cooper and McGlashan) and symptom (Manchester/Krawiecka) rating scales produce categorical data.

As far as the rating of symptoms is concerned (table 25) all the neuropsychological performances were correlated at the 1-5% level of significance with coherently expressed delusions except for spatial recognition ability. Hallucinations were related

to many of the neuropsychological performances except spatial recognition, global cognitive ability (MMSE) and number of commissions on the CPT and age scaled digit symbol substitution performance. Incoherence/irrelevance of speech was only related to age scaled digit symbol substitution performance. Education was related to incoherent affect. Finally, Rivermead scores were significantly related to both flattened affect and psychomotor retardation. There were no other significant correlations between neuropsychological performance and symptom ratings.

On the McGlashan cross sectional outcome scale (functioning in the last year) again most of the neuropsychological performances were significantly related to the individual constituents of the scale (table 26): Duration of hospitalisation except age scaled digit symbol substitution and commissions on the CPT, Employment except age scaled digit symbol substitution, Global functioning except spatial recognition, Psychopathology except age scaled digit symbol substitution, spatial recognition and present IQ. Social contact scores were again all significantly related to neuropsychological performances excluding spatial recognition memory.

The McGlashan follow-up outcome scale (present functioning) showed a similar overall connection between neuropsychological performance and constituent functional abilities (table 27). Duration of hospitalisation all except age scaled digit symbol substitution, global cognitive ability (MMSE), the Stroop test and number of commissions on the CPT. Employment all except age scaled digit symbol substitution, Global functioning all were significantly related, Psychopathology all except digit

span backwards, age scaled digit symbol substitution performance and MMSE. Social contacts were all significantly related except spatial recognition and the attention/cooperation scale.

On the Coopers social outcome scale all the neuropsychological performances were significantly related to the three components of the scale (table 28). All performances were significantly related to the degree of self care exhibited by the subjects, all performances except spatial recognition were related to social liability (the ability to maintain interpersonal relationships). As far as economic status is concerned, again most of the neuropsychological test performances were significantly related, however, this time age scaled digit symbol substitution and present IQ levels were the exceptions.

TABLE 1

DEMOGRAPHIC INFORMATION OF POOR AND GOOD OUTCOME SCHIZOPHRENIC PATIENTS (MEANS AND SDS)

	GOOD	POOR	SIGNIFICANCE
SEX	10M 10F	10M 10F	
AGE (yrs)	36.5(9.9)	34.7(10.3)	P=.577 (df=38, t=.56)
EDUCATION (yrs)	13.98(2.83)	10.93(1.17)	P<.001 (df=38, t=4.45)
ILLNESS DURATION (mths)	139.3(105.5)	150.8(106.0)	P=.732 (df=38, t=-.35)
TOTAL NO. PSYCHIATRIC ADMISSIONS	4.9(4.68)	10.45(6.49)	P<.005 (df=38,t=-3.10)
DURATION OF PSYCHIATRIC ADMISSIONS (mths)	6.65(7.07)	57.1(87.44)	P<0.002 (df=38,t=-2.57)
NEUROLEPTIC MEDICATION AT TIME OF TESTING (Chlorpromazine equivalents mgs/day)	267.9(274.1)	901.6(669.0)	P<.001 (df=36, t=-3.82)
ANTICHOLINERGIC MEDICATION AT TIME OF TESTING (Procyclidine equivalents mgs/day)	3.0(6.4)	3.3(4.7)	P=.874 (df=38, t=-.16)
DURATION OF ANTICHOLINERGIC MEDICATION (mths)	11.55(14.36)	39.8(57.39)	P=0.02 (df=38,t=-2.14)
PATERNAL OCCUPATION	2.6(.8)	2.9(.5)	LR=1.76 CHISQ=.41
MANCHESTER/ KRAWIECKA TOTALS	3.9(3.3)	11.8(5.1)	U=42.5 P<.0001

TABLE 2

GENERAL INTELLECTUAL ABILITY FOR GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS (MEANS AND SDS)

	GOOD (n=19)	POOR (n=20)		F VALUE	PROB.
			MANOVA (1,37) df	8.82	.001
NART IQ (WAIS EQUIVALENT)	114.5(10.3)	101.2(9.5)		17.65	.000
QUICK IQ	107.4(18.0)	89.1(14.9)		12.00	.001

TABLE 3

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS PERFORMANCE ON TESTS OF EXECUTIVE FUNCTIONING (MEANS AND SDS)

TEST	GOOD (n=17)	POOR (n=18)		F VALUE	PROB.
			MANOVA (1,33)df	3.33	.013
CPTF	.2(.4)	.7(1.6)		1.56	.221
CPTI	1.0 (1.4)	3.3 (3.3)		6.56	.015
STRPWC	16.7 (17.9)	41.0(19.5)		14.69	.001
TRAILS	49.8(25.6)	60.4(36.5)		.98	.329
VFLA	13.4 (7.5)	9.6(5.3)		2.97	.094
VFLB	20.2(8.7)	14.2(7.1)		4.94	.033

KEY:
CPT=CONTINUOUS PERFORMANCE TEST
F=FAILURES TO RESPOND TO AN 'E' (omissions)
I=INAPPROPRIATE RESPONSES(comissions)

STRPWC=STROOP TEST (WORD-COLOUR)

TRAILS=TRAILS(B-A) VFLA=VERBAL FLUENCY (LETTER 'A')
VFLB=VERBAL FLUENCY (ANIMALS)

TABLE 4

PROPORTION OF GOOD AND POOR OUTCOME SCHIZOPHRENIC PATIENTS REACHING CRITERION ON EACH STAGE OF THE ID/ED SET SHIFTING TEST

STAGE	GOOD (%)	POOR (%)	LIKELIHOOD RATIO	PROB.
1	19 (100)	19 (100)		
2	18 (94.7)	17 (89.5)	.37	.544
3	18 (94.7)	16 (84.2)	1.16	.281
4	18 (94.7)	15 (78.9)	2.20	.138
5	17 (89.5)	15 (78.9)	.81	.370
6	17 (89.5)	14 (73.7)	1.62	.203
7	15 (78.9)	12 (63.2)	1.16	.281
8	11 (57.9)	10 (52.6)	.11	.744
9	11 (57.9)	7 (36.8)	1.70	.192

TABLE 5

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATINETS TRIALS TAKEN TO REACH CRITERION (PER STAGE) ON THE ID/ED SET SHIFTING TASK

Comparisons based on scores of those subjects attempting stage 9.

STAGE	GOOD (n=11)	POOR (n=10)		F VALUE	PROB.
			MANOVA (1,19) df	1.74	.191
1	7.4(2.8)	11.2(6.1)		3.59	.073
2	9.6(4.2)	8.4(3.4)		.53	.475
3	7.7(2.6)	10.3(8.1)		1.00	.330
4	7.4(3.1)	9.2(5.10		1.02	.326
5	7.7(1.6)	11.0(6.5)		2.60	.123
6	6.8(1.2)	7.9(2.5)		1.65	.214
7	13.5(5.4)	17.5(14.6)		.73	.402
8	10.5(5.3)	11.7(9.4)		.14	.710
9	10.0(5.8)	26.1(20.5)		6.25	.022

TABLE 6

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS TRIALS TAKEN TO REACH CRITERION FOR SUBJECTS COMPLETING EACH STAGE OF THE ID/ED SET SHIFTING TASK

STAGE	GOOD	POOR	t(df)	PROB.
1	n=19 7.4(2.3)	n=19 10.1(6.5)	-1.72(36)	.094
2	n=18 10.2(5.9)	n=17 7.8(2.7)	1.53(33)	.135
3	n=18 7.2(2.2)	n=16 10.5(7.4)	-1.79(32)	.084
4	n=18 8.1(5.3)	n=15 10.1(7.0)	-.94(31)	.357
5	n=17 9.1(5.4)	n=15 11.9(8.9)	-1.10(30)	.281
6	n=17 6.6(1.0)	n=14 10.9(8.6)	-2.01(29)	.054
7	n=15 12.6(5.3)	n=12 16.3(13.6)	-.98(25)	.337
8	n=11 10.5(5.3)	n=10 11.7(9.4)	-.38(19)	.710
9	n=11 10.0(5.8)	n=7 15.7(14.6)	-1.18(16)	.256

TABLE 7

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS NUMBERS OF ERRORS MADE ATTEMPTING EACH STAGE OF THE ID/ED SET SHIFTING TASK

Comparisons are made between patients completing up to stage 9.

STAGE	GOOD	POOR		F VALUE	PROB.
	n=11	n=10	**MANOVA (1,19) df**	1.69	.204
1	.7(1.5)	3.2(2.8)		6.63	.019
2	2.1(1.4)	1.6(1.1)		.82	.377
3	.8(1.0)	2.3(5.0)		.94	.346
4	.5(1.2)	1.7(2.2)		2.72	.116
5	1.3(.5)	2.9(2.8)		3.61	.073
6	.6(.8)	1.0(1.3)		.58	.454
7	3.8(2.8)	6.2(7.6)		.95	.342
8	2.4(1.9)	3.3(5.3)		.30	.591
9	2.5(2.7)	9.2(10.0)		4.62	.045

TABLE 8

GOOD VERSUS POOR OUTCOME SCHIZOPHRENICS NUMBERS OF ERRORS MADE DURING THE COMPLETION OF EACH STAGE OF THE ID/ED SET SHIFTING TASK (ALL CASES)

STAGE	GOOD	POOR	t (df)	PROB.
1	n=19 .8(1.3)	n=19 2.4(3.2)	-2.06(36)	.046
2	n=18 2.4(2.5)	n=17 1.4(.9)	1.65(33)	.109
3	n=18 .6(.9)	n=16 2.5(4.5)	-1.77(32)	.087
4	n=18 .8(2.3)	n=15 1.7(2.4)	-1.03(31)	.311
5	n=17 .2.1(2.7)	n=15 3.3(4.2)	-1.02(30)	.315
6	n=17 .5(.7)	n=14 2.9(5.3)	-1.80(29)	.082
7	n=15 3.3(2.6)	n=12 5.5(7.1)	-1.14(25)	.266
8	n=11 2.4(1.9)	n=10 3.3(5.3)	-.55(19)	.591
9	n=11 2.5(2.7)	n=7 5.0(6.8)	-1.12(16)	.277

TABLE 9

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS COMPLETED SETS OF THE TOWER OF LONDON TASK(MEANS AND SDS

Univariate analyses (1,35) df.

SET	GOOD (n=19)	POOR (n=18)	F VALUE	PROB.
2	2.0(.0)	2.0(.0)	N/A	N/A
3	2.0(.0)	2.0(.0)	N/A	N/A
4	4.0(.0)	n=17 3.8(.9)	1.06	.311
5	n=18 3.8(.9)	3.6 (1.2)	.47	.497

TABLE 10

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS AVERAGE MOVES TAKEN TO COMPLETE EACH SET ON THE TOWER OF LONDON TASK(MEANS AND SDS)

Based on those patients who were able to complete at least one 5 move solution

SET	GOOD (n=18)	POOR (n=17)		F VALUE	PROB.
			MANOVA (1,33) df	2.21	.092
2	2.0(.1)	2.1(.4)		.93	.341
3	3.5(.7)	3.9(1.0)		1.57	.219
4	5.6(1.2)	6.1(.8)		1.96	.171
5	7.5(1.2)	8.7(1.5)		6.51	.016

TABLE 11

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS COMPLETING TOWER OF LONDON TASKS IN MINIMUM MOVE SOLUTIONS

SET	GOOD	POOR	FISHERS EXACT	PROB.
2	18	16		.479
3	10	5		.114
4	3	0		.125
5	1	0		.514

TABLE 12

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS MOTOR (CONTROL CONDITION) PERFORMANCE (in ms) ON THE TOWER OF LONDON TASK (MEANS AND SDS)

I) INITIATION TIME (1,33) df

SET	GOOD (n=18)	POOR (n=17)		F VALUE	PROB.
			MANOVA	.45	.770
2	2663(2236)	4001(3970)		1.53	.224
3	2178(1093)	2718(1637)		1.34	.256
4	2107(1254)	2572(1390)		1.08	.306
5	1845(806)	2138(993)		.92	.344

II) PICK UP TIME (1,33) df

SET	GOOD (n=18)	POOR (n=17)		F VALUE	PROB.
			MANOVA	1.98	.124
2	2130(1220)	2073(1275)		.02	.829
3	1744(473)	2668(1630)		5.32	.027
4	1750(628)	2030(716)		1.51	.227
5	1538(624)	1764(552)		1.27	.267

III) PLACE TIME (1,33) df

SET	GOOD (n=18)	POOR (n=17)		F VALUE	PROB.
			MANOVA	.76	.562
2	534(270)	578(193)		.31	.579
3	513(317)	637(274)		1.55	.222
4	509(202)	586(203)		1.28	.267
5	472(156)	548(150)		2.12	.155

TABLE 13

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS INITIAL PLANNING TIMES (MEANS AND SDS in ms)

SET	GOOD (n=17)	POOR (n=17)		F VALUE	PROB
			MANOVA (1,32 df)	1.12	.366
2	2054(496)	2876(423)		.86	.362
3	5895(1324)	6226(1342)		.02	.884
4	7070(426)	6226(434)		.14	.714
5	6132(536)	4795(546)		1.01	.322

TABLE 14

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS SUBSEQUENT (TO THE FIRST MOVE) PLANNING TIMES PER MOVE (MEANS AND SDS in ms)

SET	GOOD (n=17)	POOR (n=17)		F VALUE	PROB
			MANOVA (1,32 df)	.83	.516
2	251(122)	1095(112)		3.00	.093
3	1625(254)	2284(331)		.57	.457
4	2548(476)	3287(446)		.74	.397
5	1843(437)	2311(557)		.67	.418

TABLE 15

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS PERFORMANCE ON TESTS OF MEMORY (MEANS AND SDS)

TEST	GOOD (n=19)	POOR (n=19)		F VALUE	PROB.
			MANOVA (1,36) df	3.11	.01
CDMSS	9.4 (.7)	8.7 (2.0)		2.04	.161
CDMS0	8.2 (1.5)	6.6 (2.5)		5.92	.020
CDMS4	7.8 (1.2)	6.7 (2.5)		3.22	.081
CDMS12	6.7 (1.7)	5.6 (1.9)		4.01	.053
CPRT	19.3 (4.1)	17.8 (3.0)		1.51	.228
CSRT	15.4 (2.3)	13.6 (3.0)		4.48	.041
DSFR	7.5 (1.4)	7.3 (1.2)		.42	.521
DSBR	5.3 (1.9)	3.7 (1.3)		9.09	.005
RPT	21.7 (1.9)	17.3 (3.8)		20.26	.000

CDMSS=DELAYED MATCHING TO SAMPLE SIMULTANEOUS CONDITION
CDMS0=0 SEC DELAY
CDMS4=4 SEC DELAY
CDMS12=12 SEC DELAY
CPRT=PATTERN RECOGNITION TEST
CSRT=SPATIAL RECOGNITION TEST
DSFR=DIGIT SPAN FORWARDS
DSBR=DIGIT SPAN BACKWARDS
RPT= RIVERMEAD PROFILE SCORES

TABLE 16

SCORES ON THE SUBTESTS OF THE RIVERMEAD BEHAVIOURAL MEMORY TEST FOR GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS (MEANS based on raw scores)

SUBTEST	GOOD (n=19)	POOR (n=20)		F VALUE	PROB.
			MANOVA (1,37 df)	3.02	.008
FIRST NAME	1.9	1.5		3.35	.075
SECOND NAME	1.8	1.4		3.65	.064
BELONGING	3.3	3.0		.64	.429
APPOINTMENT	1.8	1.4		4.57	.039
PICTURE RECOG-NITION	9.9	9.6		2.76	.105
STORY IMMEDIATE	8.7	5.0		12.58	.001
STORY DELAYED	7.8	3.8		14.83	.000
FACE RECOGNITION	4.8	4.7		1.08	.305
ROUTE IMMEDIATE	4.9	4.9		.00	.958
ROUTE DELAYED	4.8	4.8		.11	.740
MESSAGE IMMEDIATE	3.0	2.6		5.34	.027
MESSAGE DELAYED	2.9	2.6		4.78	.035
ORIENTATION	8.9	8.2		7.28	.010
DATE	.9	.8		.65	.426
TOTAL	64.9	53.7		22.06	.000

TABLE 17

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS PERFORMANCE ON LATERALISATION TESTS (MEANS AND SDS)

TEST	GOOD (n=18)	POOR (n=19)		F VALUE	PROB.
			MANOVA (1,35) df	1.37	.265
LCT	-.1(.8)	-.4(.6)		1.25	.271
SCT	.2(.4)	.0(.6)		.77	.387
XLINE	-4.7 (8.0)	1.9 (15.3)		2.66	.112

LCT=LETTER CANCELLATION TEST
SCT=STAR CANCELLATION TEST
XLINE=LINE BISECTION TEST

TABLE 18

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS PERFORMANCE (in ms) ON TESTS OF PSYCHOMOTOR ABILITY (MEANS AND SDS)

TEST	GOOD (n=19)	POOR (n=18)		F VALUE	PROB.
			MANOVA (1,35) df	2.83	.053
CRTML5	599.6 (168.2)	692.1 (256.9)		1.70	.201
CRTRL5	374.9 (109.0)	424.1 (122.8)		1.66	.205
DSS	8.6 (2.4)	6.4 (2.0)		8.87	.005

CRTML5=MOVEMENT LATENCY STAGE 5 (CANTAB)
CRTRL5=REACTION LATENCY STAGE 5 (CANTAB)
DSS=DIGIT SYMBOL SUBSTITUTION TEST AGE SCALED SCORES

TABLE 19

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS ATTENTION AND CO OPERATION SCORES (INVESTIGATOR ASSESSMENT) (MEANS AND SDS)

SCALE	GOOD (n=19)	POOR (n=20)		F VALUE	PROB.
			MANOVA (1,37)df	5.04	.012
ATTENTION	4.7(.6)	3.9(1.1)		8.3	.006
COOPERATION	4.5(.5)	4.2(.8)		9.08	.005

TABLE 20

CORRELATIONS BETWEEN NEUROPSYCHOLOGICAL TEST PERFORMANCE AND YEARS OF FULL TIME EDUCATION

TEST	r	TEST	r	TEST	r
NART IQ (WAIS EQUIV.)	.6980**	CTLAM5	-.4328**	RPT	.4381**
QUICK IQ	.4777**	CDMSS	.1977	LCT	.0104
MMSE	.3858*	CDMS0	.3804*	SCT	-.0899
CPTF	-.1474	CDMS4	.2984	XLINE	-.0936
CPTI	-.3638*	CDMS12	.3570*	CRTML5	-.2484
STRPWC	-.6326**	CPRT	.0767	CRTRL5	-.2585
TRAILS	-.3963*	CSRT	.3678*	DSS	.5564**
VFLA	.4222**	DSF	.3109	RAT	.2874
VFLB	.4815	DSB	.5444**	RCT	.2253

*P<.05 **P<.01

TABLE 21

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS PERFORMANCE ON TESTS OF EXECUTIVE FUNCTIONING CONTROLLING FOR FULL TIME YEARS OF EDUCATION (MEANS AND SDS)

TEST	GOOD (n=17)	POOR (n=18)		F VALUE	PROB.
			MANCOVA (1,33)df	1.27	.304
CPTF	.2(.4)	.7(1.6)		.87	.359
CPTI	1.0 (1.4)	3.3 (3.3)		2.36	.135
STRPWC	16.7 (17.9)	41.0(19.5)		2.46	.127
TRAILS	49.8(25.6)	60.4(36.5)		.32	.575
VFLA	13.4 (7.5)	9.6(5.3)		.08	.780
VFLB	20.2(8.7)	14.2(7.1)		.32	.576

TABLE 22

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS PERFORMANCE ON TESTS OF MEMORY CONTROLLING FOR FULL TIME YEARS OF EDUCATION(MEANS AND SDS)

TEST	GOOD (n=19)	POOR (n=19)		F VALUE	PROB.
			MANCOVA (1,36) df	1.34	.262
CDMSS	9.4(.7)	8.7(2.0)		.73	.399
CDMS0	8.2(1.5)	6.6(2.5)		1.38	.247
CDMS4	7.8(1.2)	6.7(2.5)		.67	.419
CDMS12	6.7(1.7)	5.6(1.9)		.63	.435
CPRT	19.3(4.1)	17.8(3.0)		1.38	.248
CSRT	15.4(2.3)	13.6(3.0)		.76	.390
DSFR	7.5(1.4)	7.3(1.2)		.44	.514
DSBR	5.3(1.9)	3.7(1.3)		1.08	.306
RPT	21.7(1.9)	17.3(3.8)		9.72	.004

TABLE 23

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS PERFORMANCE ON TESTS OF PSYCHOMOTOR FUNCTIONING(in ms) CONTROLLING FOR FULL TIME YEARS OF EDUCATION (MEANS AND SDS)

TEST	GOOD (n=19)	POOR (n=18)		F VALUE	PROB.
			MANCOVA (1,34) df	.37	.773
CRTML5	599.5 (168.2)	692.1 (256.9)		.24	.625
CRTRL5	374.9 (108.9)	424.1 (122.8)		.19	.667
DSS	8.6(2.4)	6.4(2.0)		1.51	.291

TABLE 24

GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS ATTENTION AND CO OPERATION (AT TIME OF TESTING) CONTROLLING FOR FULL TIME YEARS OF EDUCATION (MEANS AND SDS)

SCALE	GOOD (n=19)	GOOD (n=20)		F VALUE	PROB.
			MANCOVA (1,36) df	3.38	.045
ATTENTION	4.7(.6)	3.9(1.1)		4.54	.040
CO-OPERATION	4.8(.5)	4.2(.8)		6.73	.014

TABLE 25

SPEARMANS CORRELATIONS OF NEUROPSYCHOLOGICAL PERFORMANCES SHOWING GROUP DIFFERENCES FOR GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS AGAINST MANCHESTER/KRAWIECKA SCORES

TEST	SYMPTOMS								
	DP	**AX**	**CED**	**H**	**IS**	**PS**	**FA**	**IA**	**PR**
CSRT	.0710	.2028	-.2147	-.1995	-.0958	-.1000	.1464	.2323	-.0480
DSBR	-.0527	-.0776	-.3865**	-.3385*	-.0715	.2056	.0491	-.2340	.0266
DSS	.0757	-.0222	-.3336*	-.2546	-.3083*	-.0003	.1594	.0217	.1245
EDUC	.1071	.0509	-.4628***	-.2913*	-.1467	-.1296	-.1462	-.2666*	-.0765
MMSE	.1606	-.0613	-.3862**	-.2189	-.0350	.2074	-.0356	.0396	-.0017
N(WAIS)	.0695	-.0581	-.4535**	-.3769**	-.2251	-.0125	-.0069	-.1534	.0117
QIQ	.0778	.0546	-.4461**	-.4401**	-.2085	-.0350	-.0100	-.0064	-.1117
RATS	.1019	.0730	-.3417*	-.3580**	-.1147	-.0211	.1423	.1958	-.0414
RCT	-.1020	-.1264	-.4153**	-.3923**	-.0738	-.0446	.1143	.1404	-.0437
RPT	-.0236	.0515	-.5416***	-.4182**	-.1288	-.1818	-.2696*	-.0300	-.3281*
STRPWC	.0819	-.0919	.4580**	.3947**	.2078	.0962	.1283	.0234	.1837
VFLB	-.2482	-.2508	-.4868***	-.4133**	-.0849	.0004	-.0605	-.1120	-.0773
CPTI	-.0480	.1024	.3647*	.2297	.2062	.0006	.0046	.0185	.0476

* P<.05 ** P<.01 ***P<.001

KEY:DP DEPRESSION
H HALLUCINATIONS
AX ANXIETY
IS INCOHERENT/IRRELEVANT SPEECH
PR PSYCHOMOTOR RETARDATION
PS POVERTY OF SPEECH
IA INCONGRUOUS AFFECT
CED COHERENTLY EXPRESSED DELUSIONS

TABLE 26

SPEARMANS CORRELATIONS OF NEUROPSYCHOLOGICAL PERFORMANCES SHOWING GROUP DIFFERENCES FOR GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS AGAINST Mc GLASHAN (OUTCOME) SCORES

TEST	FACTORS					
	MCD	**MCE**	**MCG**	**MCP**	**MCS**	**MCT**
CSRT	.3776**	.3740**	.2087	.1812	.0952	.3160*
DSBR	.3971**	.3967**	.3532*	.3477*	.4301**	.4737***
DSS	.1956	.2455	.3174*	.2096	.3259*	.3120*
EDUC	.4401**	.4443**	.4738***	.3720**	.4749***	.5104***
MMSE	.3934**	.3531**	.3551*	.3716**	.4459**	.4791***
N(WAIS)	.4353**	.3862**	.4367**	.2776*	.5675***	.5077***
QIQ	.3008*	.4051**	.3981**	.2634	.5394***	.4480**
RATS	.4510**	.4885***	.4282**	.3214*	.2117	.4470***
RCT	.4293**	.4809***	.5030***	.3901**	.3723**	.5534***
RPT	.5193***	.5886***	.5763***	.5029***	.4115**	.6216***
STRPWC	-.3025*	-.5400***	-.4939***	-.3467*	-.5442***	-.5573***
VFLB	.2982*	.4347**	.4762***	.3901**	.5090***	.4661***
CPTI	-.2534	-.3549*	-.2703*	-.3472*	-.3822**	-.4148**

* P<.05 **P<.01 ***P<.001

KEY:

D DURATION OF HOSPITALISATION
E EMPLOYMENT
G GLOBAL FUNCTIONING
P PSYCHOPATHOLOGY
S SOCIAL CONTACTS
T TOTALS

TABLE 27

SPEARMANS CORRELATIONS OF NEUROPSYCHOLOGICAL PERFORMANCES SHOWING GROUP DIFFERENCES FOR GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS AGAINST McGLASHAN (FOLLOW-UP) SCORES

TEST	FACTORS					
	MCD	**MCE**	**MCG**	**MCP**	**MCS**	**MCT**
CSRT	.3939**	.3477*	.3130*	.3144*	.0699	.3574*
DSBR	.3549*	.3339*	.3945**	.1531	.3323*	.3685**
DSS	.1885	.0716	.3214*	.2561	.3148*	.2312
EDUC	.4552**	.3145*	.4820***	.3799**	.3997**	.4773***
MMSE	.1952	.3532*	.3317*	.2363	.3606*	.3374*
N(WAIS)	.4505**	.2723*	.4328**	.2941*	.4727**	.4521**
QIQ	.3097*	.3046*	.4093**	.2817*	.4899**	.4254**
RATS	.3689**	.4575**	.4368**	.3151*	.2629	.4356**
RCT	.3592*	.5073***	.4724***	.3379*	.4183**	.5200***
RPT	.4572**	.4948***	.5137***	.5729***	.3146*	.5651***
STRPWC	-.2768	-.4775**	-.5102***	-.3194*	-.4915***	-.4848**
VFLB	.3827**	.3336*	.4207**	.4222**	.4134**	.4656***
CPTI	-.1911	-.2951*	-.3252*	-.2741*	-.2949*	-.3234*

* P<.05 **P<.01 *** P<.001

TABLE 28

SPEARMANS CORRELATIONS OF NEUROPSYCHOLOGICAL PERFORMANCES SHOWING GROUP DIFFERENCES FOR GOOD VERSUS POOR OUTCOME SCHIZOPHRENIC PATIENTS AGAINST COOPERS SOCIAL OUTCOME SCALE SCORES

TEST	FACTORS			
	SELF-CARE	**ECONOMIC**	**SOCIAL LIABILITY**	**TOTAL**
CSRT	.3991**	.3590*	.2574	.3722*
DSBR	.3816**	.2717*	.4146***	.4405**
DSS	.4293**	.2323	.4772***	.4126**
EDUC	.5501***	.4808***	.5226***	.5942***
MMSE	.4616**	.2740*	.4439***	.4772***
N(WAIS)	.5158***	.2771*	.5690***	.5300***
QIQ	.4939***	.2366	.5348***	.4803***
RATS	.4523**	.3095*	.4450**	.4688***
RCT	.4881***	.3329*	.5152***	.53938***
RPT	.6598***	.4733***	.5995***	.6537***
STRPWC	-.5241***	-.4770**	-.5630***	-.6308***
VFLB	.3795**	.3420*	.4265**	.4457**
CPTI	-.4279**	-.2892*	-.4632**	-.4883***

* P<.05 **P<.01 ***P<.001

6.4 DISCUSSION

The aim of this study was to analyse which neuropsychological impairments discriminate between a group of schizophrenic patients dichotomised by outcome. The patients were selected according to their degree of treatment response, social and vocational status, and symptom profiles. Careful recruitment resulted in two groups well matched for sex, age and duration of illness. The two groups were coined good outcome (treatment responsive) and poor outcome (treatment unresponsive/resistant) patients. It was no surprise that the poor outcome patients had spent significantly longer in hospital, had more psychiatric admissions and were currently on higher doses of neuroleptics (and experienced longer periods on anticholinergic medication) than the good outcome patients. Of particular importance was the significant discrepancy in terms of number of full time years of education experienced by the two groups, in favour of the good outcome patients. Because of the close relation of education level and neuropsychological performance (Lezak, 1983), this discrepancy needed to be accounted for in the analysis and interpretation of the neuropsychological test performances of the two groups. This will be discussed with relevance to the emergent results later.

The neuropsychological analysis comprised of testing the two groups with a large battery of tests encompassing the functional domains of general intellectual level, executive functioning, memory functioning, psychomotor ability and degree of hemispatial neglect. Associations of the neuropsychological data were analysed with

respect to the symptom and functional outcome scales used in selection of the patient samples. Statistical analysis was performed using multiple comparisons to account for the large amount of neuropsychological data obtained from the individual tests under the general functional domains cited above. Although this was something of an exploratory exercise, the domains of cognitive functioning investigated were consistent with those currently implicated as underpinning the behavioural phenomena of schizophrenia (see Methods). The implications of such an exercise ought to expose particular areas of impairment, over general impairment, that are closely associated with outcome status which may provide an emphasis for the future of cognitive analysis of outcome and/or raise issues for treatment or neurorehabilitation of those patients who are presently not responding to current therapies.

The comparative analysis of the neuropsychological performances of the two outcome groups provided significantly different levels of functioning in the domains of general intellectual ability, executive functioning and memory functioning. Although there was no overall difference in psychomotor ability, individual test performance analysis indicated a significant difference on a timed visuo-spatial coding test. No differences were observed on the groups degree of hemispatial neglect. All the significant differences recorded attested to the superior performance of the good outcome patient group over the poor outcome patient group. It may be argued that the poor outcome group might be expected to do poorly on a wide range of tests compared to remitted patients, due to their general illness status affecting motivation. To account for this, a subjective analysis of motivation in terms of attention/

cooperation was recorded by the examiner at testing. This crude appraisal indeed did show a significant demotivated state of the poor outcome patients. Whether demotivation arises from the illness state, duration of hospitalisation or drug effects is uncertain, however, all were experienced at elevated levels in the poor outcome group. Although these issues ought to be recognised in the interpretation of the neuropsychological results, it may well be that it is the putative neuropsychological impairments of the poor outcome group that account for the problems in attending and cooperating with demanding testing.

Both pre morbidly and currently, the poor outcome patients displayed significantly depressed levels of general intellectual ability. Recently, however, the standard measure of pre morbid ability, the NART, has been shown as possibly compromised by the disease process in groups of long term hospitalised schizophrenic patients (i.e. poor outcome patients), not observed in community based schizophrenic patients (Crawford et al., 1992). It might be safe to assume that the present study's outcome groups mirrored the Crawford et al.'s samples. To clarify the pre morbid status of the two outcome groups, avoiding possible illness effects, a crude measure of paternal occuapational status was used to assess pre morbid status in terms of socio-economic background. This, of course, was not a neuropsychological analysis but was useful in confirming that there was no difference in social advantage between the two groups. Thus, we might conclude, with caution, that any emergent difficulties in neuropsychological performance (and, indeed, in educational experience) did not arise from a disparity in pre morbid status as assessed by social background. However, one

interprets the validity of NART performance with regard to the poor outcome patients, whether affected by the illness process or not, the two groups can be differentiated on their ability to perform the NART and also show differing levels of current intellectual ability in favour of the good outcome patients. Again these results need to be accounted for in the interpretation of any neuropsychological performance differences between the two groups as they may products of general intellectual (dis)ability.

From the initial analyis of the wealth of neuropsychological data obtained, there appeared to be a pattern of neuropsychological impairment that discriminated between the groups, indicating a particular pattern of impairment associated with poor outcome. The cognitive profile of the poor outcome group was characterised by particular deficits in executive and memory functioning. It has been established that both heterogeneous group studies (Kolb and Wishaw, 1983) and single case reports (Shallice et al., 1991) have implicated 'frontal' type dysfunction or a dysexecutive syndrome in schizophrenia. These deficits have been linked to a difficulty in the self generation activity and/or organising information for environmentally appropriate behaviour (Shallice, 1988; Frith, 1992). In this study, the poor outcome patients displayed specific executive impairment on tests involving sustained attention and the inability to suppress inappropriate responding (i.e. disinhibition). There was also a significant impairment on word production ability when defined by a semantic category rather than by an initial letter paradigm. Difficulties with tests involving inhibitory processes have been associated with symptoms of incongruity and

incoherence (Liddle and Morris, 1991; Frith et al., 1991). However, there was no significant association in this study. Again, although poor verbal fluency has been associated with psychomotor poverty type symptoms (Liddle and Morris, 1991) here it was neither related to poverty of speech nor psychomotor retardation symptoms. The present test results were related to coherently expressed delusions and hallucination symptom ratings. Although, disorganisation type cognitive impairments are not usually associated with abnormal experiences (Liddle, 1987; Liddle and Morris, 1991), the present relationship between symptoms could be explained in terms of a combination of disinhibition along with poor word access/retrieval from a semantic memory system. A similar process of cognitive impairment has already been suggested to account for the expression of positive symptomatology in schizophrenia. Gray et al., (1991) suggested that the inability to inhibit all but relevant memories from current behaviour could result in delusional and hallucinatory experiences through the inability to use specific, appropriate, learned behaviours in current functioning. Of course, the association between these symptoms and the impaired neuropsychological performances could be due to delusions and hallucinations (along with psychomotor retardation) being the only symptom ratings between the groups. This does not detract from the pattern that underlying such symptoms are, at least in part, the specific executive impairments observed here.

Implied in the above conclusions is that some memory access or organisation of memory processing systems might be connected with the abnormal experiences that define the poor outcome patients. The analysis of the memory performance of the

outcome groups did expose particular poor memory dysfunction on the part of the poor outcome patients. Of note was the poor episodic memory functioning of the poor outcome patients characterised by poor recall (immediate and delayed) memory rather than recognition memory. In addition, poor short term working, in terms of repeating digit sets backwards, discriminated between the groups in favour of the good outcome patients. Recognition memory in terms of the short term computerised tests did not discriminate between the groups with regard to pattern and delayed matching to sample (except in the later's case for 0 sec delay), but the poor outcome patients did display poorer short term spaital recognition memory than the good outcome patients. Therefore, memory functioning discriminated between the outcome groups according to short term auditory and spatial recognition memory and immediate and delayed recall on an episodic memory test, the poor outcome group displaying the markedly depressed functioning. From these results one can conclude that poor outcome in schizophrenia may well be characterised by gross memory difficulties, along with impaired inhibitory capability and verbal fluency demanding semantic access/retrieval. Memory difficulties have been recently highlighted as characteristic of heterogeneous groups of schizophrenic patients, disproportionate to the level of general intellectual impairment (McKenna et al.,1990; Tamlyn et al., 1992), the effect has been also observed with neuroleptic naive patients (Saykin et al., 1991). The former two studies found a particular deficit in episodic memory functioning, as assessed by the Rivermead Behavioural Memory Test, as used in the present study. However, it is unclear what pattern of dysfunction characterised these impairments as no breakdown of subtest scores was available. The Rivermead scores

and the short term working memory performances were, like the executive discriminants, associated with coherently expressed delusions and hallucinations. There may be emerging a pattern of neuropsychological deficits charaterised by particular executive and memory dysfunction that, when coexisting, may underpin the formation of the positive symptoms of schizophrenia, and dependent on the degree to which these impairments are expressed may characterise the stubborness of these symptoms to available therapies and form the basis of poor outcome. The link between the executive and episodic memory deficits expressed in the present study might have basis in the interdepentability of episodic and semantic memory systems (Tulving, 1983). Aswell as episodic impairments, semantic memory difficulties have been implicated in the formation of delusional and hallucinatory behaviour (McKenna, 1991; Hoffman, 1987). McKenna (1991) has indicated that delusions arise from an impairment in the continuous gathering and reality checking of knowledge so that false memories are laid down which become delusions. This , in turn, would imply a deficit in both semantic and episodic memory systems. Cutting and Murphy (1988) suggested, at the heart of delusions and formal thought disorder, there was a deficiency in real world knowledge. In turn, Frith (1992) has proffered a universal deficit in the systems that represent knowledge as underpinninng all positive and negative symptoms of schizophrenia. As stated above, Gray et al. (1991) proposed a specific deficit in the access appropriate stored memories for minute to minute appropriate functioning in the formation of positive symptoms. The results here would suggest that, not only do they support a fundamental memory impairment in schizophrenia as a whole, but that patients who have been carefully selected, along

clinical and everyday functioning scales, to be of poor outcome are especially characterised by these neuropsychological deficits. The combination of inhibitory deficits, semantic memory access/retrieval and episodic memory functioning (as well as short term memory problems) would support the kind of theoretical standpoint associating fundamental memory difficulties, and importantly, the appropriate utilisation of stored memories, in the formation of the characteristic positive signs of schizophrenia.

As stated above, there was a large discrepancy in the education background of the two outcome groups, the good outcome patients experiencing significantly more full time years of education than the poor outcome counterparts. It has already been established that poor outcome is characterised by early and insidious onset of illness (Lieberman and Sobel, 1993). A difference in education background, therefore might not be unexpected. Jones et al. (1993) observed that poor outcome, in terms of social and occupational status, is associated with poor educational qualifications. To assess whether the large difference in education affected the neuropsychological performance between the two groups, the multivariate analysis was repeated controlling for education. In a preliminaer analysis, the discriminating neuropsychological performances were all, bar semantic verbal fluency, significantly correlated with education background. When education had been controlled for, the executive significant differences disappeared as did the majority of the memory performance differences. However, despite the influence of the disparity in education, the groups were still significantly differentiated on episodic memory performance, still

at a high level of significance. Subjective attention/cooperation ratings were also still significantly different in favour of the good outcome patients. The robust status of episodic memory as characteristic of poor outcome was supported when present intellectual functioning, anticholinergic duration and present levels of neuroleptics had been controlled for, the highly significant between group difference remaining. However, there was an indication that episodic memory performance might be influenced by long term hospitalisation. It may not be surprising that episodic memory performance was not grossly influenced by education or current intellectual factors as, in the original conception of the test, it was designed to avoid just such factors (Wilson et al., 1985).

A picture, therefore, emerged that either poor outcome schizophrenia was characterised by a combination of particular executive and memory dysfunction or that, compensating for the difference in education background, it was episodic memory dysfunction alone that discriminated between the two outcome groups. It would, however, appear that episodic memory dysfunction is the most robust neuropsychological discriminant of outcome, from the present results. A problem in leaving our conclusions there is that researchers have tended to associate long term chronic medicated schizophrenic functioning with primarily 'frontal' or executive dysfunction (Shallice et al., 1991; Weinberger et al., 1988). In addition, the emergent emphasis on memory dysfunction has been suggested as secondary to 'frontal'impairment (Goldberg et al., 1989). The debate, between which impairment is of primary importance in underpinning schizophrenic symptoms, rages on. It cannot

be ignored that one might expect executive impairments characterising a group of poor outcome patients' functioning as many of the everyday fucntioning that defines them as poor outcome obviously involves some degree of impaired organisational, planning and scheduling activity i.e. fundamental executive abilities. A criticism, of the executive tests widely used in neuropsychological studies, is that they do not relate to the planning and organisational demands faced in everyday functioning (Shallice et al., 1991). Shallice and Burgess (1991) have proposed more ecologically valid tests e.g. the Six Elements Test that requires the subject to organise behaviour over a longer period of time than traditional tests. The same authors showed that 'frontal' patients, who showed normal functioning on standard tests of executive functioning, nevertheless showed impaired performance on this more everyday related test of planning ability. This approach might prove useful in further studies of associating neuropsychological deficits with outcome in schizophrenia.

The implications of the above results should be assessed with regard to the type of neurorehabilitation resources offered to patients with persistent psychopathology and impaired social and vocational functioning. Mueser et al. (1991) have already highlighted that with heterogeneous groups of schizophrenic patients, both baseline social skills deficits and rate of social skill acquisition in a training programme were associated with severity of memory impairments. If poor outcome patients have particularly poor episodic memory dysfunction then, for instance, social functioning may be optimised by focussing on social skill acquisition, compensating for the neuropsychological disadvantage that such patients appear to be suffering from. In

addition, both vocational and social dysfunctioning implicate cognitive problems involving problem solving in novel situations and utilising memory appropriately in the correct environment (Jaeger et al., 1992). Future neuropsychological studies ought to investigate the incidence and degree of such impairments using both executive and memory measures of ecological validity, that would, in turn, aid therapists and doctors that have been faced with a substantial proportion of schizophrenic patients as yet unresponsive to contemporary rehabilitation techniques.

CHAPTER 7: GENERAL DISCUSSION

7.1 Restatement of the aims of the thesis

This thesis attempted to provide an explanation of schizophrenic behaviour, in terms of underlying cognitive processes, through neuropsychological assessment. As schizophrenia is presently considered a heterogeneous condition, neuropsychological functioning was analysed with respect to symptom expression. The neuropsychological assessments were carried out with respect to illness duration, medication status and treatment response or outcome status. The methodology for the investigations involved neuropsychological testing using traditional (e.g. Stroop and verbal fluency tests) and novel measures (e.g. computerised Intra-and Extradimensional Set Shifting and Tower of London tests from CANTAB). The measures were chosen to assess executive, memory, psychomotor functioning and hemispatial neglect. Deficits in all three domains have been implicated as characteristic of functioning in various groups of schizophrenic patients. The relationship between these functional deficits and particular symptoms or groups of related symptoms has been less well documented. These areas of neuropsychological functioning were analysed with respect to symptoms and medication status involving high and standard doses of typical neuroleptic medication and the atypical neuroleptic, risperidone, with historically treatment resistant patients. The relationship between poor outcome schizophrenia and neuropsychological test performance was also assessed.

7.2 Symptoms and illness duration

Factor analysis of symptom ratings from the Positive and Negative Syndrome Scale (Kay et al., 1986) generated different sub syndromes of related symptoms between acute and chronic stages of schizophrenic illness. In the study involving a large sample of chronic schizophrenic patients sub syndromes relating to reality distortion, poverty of sociability and affect, disorganisation and excitability (grandiosity/hostility) emerged from the factor analysis. These sub syndromes related closely to Liddle and Barnes (1990) three sub syndrome model of schizophrenic symptomatology, but, due to the composition of the PANSS rating scale an extra sub syndrome of symptoms, indicating a sub pathology of 'overarousal', emerged. The presence of this extra sub syndrome might be due to the limitations of the Liddle et al. rating scales, different types of chronic patients in the respective studies-the present study used a large sub population of treatment resistant patients whose illnesses might have been less stable than the Liddle et al. sample, or might represent a further valid independent sub pathology of illness present at the chronic stage of illness. Recently, researchers have indicated that if symptoms that reflect the affective and 'overarousal' features of the illness are added to the analysis, two further sub syndromes of depression and psychomotor excitation emerge (Liddle, unpublished data cited in Liddle et al., 1994). The latter of these sub syndrome may have much in common with the excitability sub syndrome from the present study.

At the acute stage of illness five factors or sub syndromes reflecting paranoid state, poverty of affect, disorganisation and poverty of sociability and delusions emerged. The number of acute stage schizophrenic patients' symptom ratings entered for analysis was small and, thus, the endeavour was considered a preliminary investigation of symptom expression at this stage of illness. A major caveat in the interpretation of such sub syndromes of illness was that the patient sample, by definition, consisted of floridly ill patients whose symptom profile might be extremely variable from day to day, thus not rendering reliable associations between symptoms. Therefore, the emergent sub syndromes might be invalid as indicators of independent sub pathologies of schizophrenia characteristic of this stage of illness. Despite this, the emergent sub syndromes could be demonstrating that different sub pathologies of illness are present at the early stage of illness than the chronic stage.

The process of factor analysing symptom rating scales does help overcome the heterogeneity of the schizophrenic condition. However, it is an empirical process that produces factors based entirely on which symptoms are entered into the analysis and what meaning the investigator attaches to the emergent factors (Bentall et al., 1988). Also, Frith (1992) suggested that, before entering specific symptoms into the factor analysis, one ought to have an idea of what clusters are likely based on a theory of underlying cognitive deficits. Bentall et al. (1988) criticised factor analytic studies for being biased toward highly symptomatic hospitalised samples, therefore giving inflated correlations between symptoms unrepresentative of schizophrenic patients as a whole. In the present thesis it would appear that different samples, selected by stage

of illness, do display different relations between symptoms and, thus, indicate different sub pathologies of illness at different stages of illness. It is necessary, however, that emergent factors should be meaningful, not only in terms of face validity, but that constituent symptoms ought to be predicted to co-exist due to common underlying dysfunctional cognitive processes.

7.3 Sub syndromes and neuropsychological functioning

The sub syndromes of poverty of sociability and affect and disorganisation were directly related to impaired short term working memory and episodic memory ability at the chronic stage of illness. There was also evidence to suggest that a semantic accessing difficulty was associated with poverty of sociability and affect, and that executive difficulties, involving response inhibition, were related to disorganisation, but were also related to global intellectual levels of functioning. The sub syndromes of reality distortion and grandiosity/hostility, representative of abnormal experiential behaviour were not directly related to neuropsychological performance. At the acute stage of illness no direct relation of neuropsychological performance was observed with any of the emergent sub syndromes. This inability to relate sub syndromes to neuropsychological functioning might also reflect the instability of symptom expression in this group and support the invalidity of the emergent factors as representing stable sub pathologies of illness at this stage.

Both acute and chronic populations showed impaired functioning compared to healthy controls across executive, memory and psychomotor functioning domains. The chronic patients showed equivalent hemispatial functioning compared to the control group, possibly due to the 'normalising' effect of long term medication. The patients in both groups were impaired on the executive, memory and psychomotor tests despite intact global pre morbid and current intellectual levels. However, there was a difference in the number of full time years of education between chronic patients and controls but not between acute patients and controls. Educational disadvantage was highlighted as characteristic of poor outcome in Chapter 6. This would imply that the chronic group consists of patients of poor outcome and that the acute group would consist of patients, conservatively, of mixed prognosis. The different groups may comprise different types of patients, which may explain, in part, the difference in sub syndrome expression derived from the factor analysis.

A pattern emerged that both chronic and acute patient groups were functioning below normal limits on a wide range of neuropsychological tests. Impairment was only directly related to poverty of sociability and affect and disorganisation at the chronic stage. Neither sub syndromes comprising of abnormal experiences, at the chronic stage, nor all of the sub syndromes, at the acute stage, were directly associated with neuropsychological performance. Therefore, the sub syndromes not related directly to neuropsychological functioning were seen as being underpinned by neuropsychological dysfunction as a secondary phenomenon to other more complex

mediating psychological processes more closely related to the symptom groups in question.

As far as the direct relationships between sub syndromes and neuropsychological functioning are concerned, the association between poverty of sociability and affect with poor short term and episodic memory might be explained by poor social cognition. Poor social cognition could be due to a depleted store of appropriate social knowledge due to poor developmental social experiences. Also, the inability to infer others' beliefs and intentions, in the social arena, might be due to an inability to apply appropriate old memories to cope with novel situations, therefore, resulting in impoverished social encounters. Studies have shown that schizophrenic patients are impaired in appropriately distinguishing and labelling emotional expressions (Gessler et al., 1989) i.e. incorrectly inferring non-verbal information crucial for engaging in appropriate social behaviour. The inability to infer others intentions and beliefs, and one's own intentions, in terms of generating spontaneous willed action, has been proposed as underlying many of the behavioural phenomena of schizophrenia (Frith, 1992). This has been coined lacking a 'theory of mind' or an impairment in metarepresentation where awareness of one's own and others goals and willed intentions is crucial for self-awareness. Without such an ability appropriate social and affective behaviour would be extremely difficult due to a basic poverty of communication between the schizophrenic patient and their environment. Within the present context of poor social relations, the episodic memory dysfunction is the prime candidate for the neuropsychological mechanism that contributes to this inability for

conscious awareness. Episodic memory dysfunction was primarily associated with disorganisation at the chronic stage of illness, although executive dysfunction involving disinhibition was implicated as related to this sub syndrome. This relation is due to a possible dysfunction in the organisation and temporal ordering of appropriate information for recall, reminiscent of frontal lobe amnesia (Shallice, 1988). However, one would have to examine the content of such recall for confirmation.

As stated above, the sub syndromes of reality distortion and excitability, at the chronic stage of illness, and the sub syndromes of paranoid state, grandiosity and (other) delusions, at the acute stage, could not be directly explained by neuropsychological impairment on testing. The formation of such sub syndromes was thought, speculatively to have some theoretical basis in the work of Richard Bentall (1994) and his model of the formation of paranoid delusions. This speculation was pursued on account of three major reasons. Firstly, the paranoid state at the acute stage was characterised by hostility, excitement, suspiciousness/persecution, poor rapport and hallucinations and appeared to contain not only abnormal experiential phenomena but, also, how such thinking would be expressed, behaviourally, in the patient's immediate environment. Secondly, paranoid and grandiose behaviour has been suggested as different manifestations of the same underlying cognitive bias in Bentall's (1994) model. Thirdly, the obvious neuropsychological impairments expressed by both groups, compared to controls, might underpin the more primary cognitive abnormalities responsible for the expression of the abnormal experiential sub syndromes, in concert with other environmental and personal factors. In Bentall's

model paranoid and grandiose delusions derive from a cognitive bias in the schizophrenic patient's information processing in an attempt to cope with feelings of low self esteem and perceived stress in one's environment. Persecutory beliefs arise from the patient attributing positive events to the self and negative events to the environment (Kaney and Bentall, 1989). Poor social cognition may also play a part in this process through the misinterpretation of others' intentions and beliefs in a negative self-referential manner (or positive in the case of grandiose beliefs). Poor social cognition, characterised by difficulties in social inference, again reflects a lack of 'theory of mind' which Frith (1992) suggests underpins most schizophrenic symptomatology. The lack of awareness of social convention and inference would imply a poverty of executive and memory functioning, which was expressed by the acute and chronic groups. An executive dysfunction would impair the choice of appropriate behavioural schema in novel situations. Memory dysfunction, characterised by impaired episodic memory, would result in a inability to access contextually specific social information, whether stored or not, for use in routine or novel situations. The inability to access contextually specific information might serve to enhance the paranoid belief system of the persecuted patient, as disconfirmatory evidence would not be forthcoming to annul the initial threat felt in a social situation. Future assessments of such abnormal experiences should look further than trying to find neuropsychological correlates of these type of symptoms. The behaviour derives from an individual, with certain fundamental neuropsychological impairments, who, despite these deficits, has to make sense of their social universe and form belief systems that help coping. Unfortunately, it appears that the protection of the self,

through persecutory belief systems, is born of a coping strategy underpinned by faulty neuropsychological functioning and serves to alienate the individual from an already perceived hostile environment.

7.4 Medication, symptoms and neuropsychology

The analysis of neuropsychological functioning of a group of historically treatment resistant schizophrenic patients was undertaken within a controlled drug trial involving optimum doses of standard (chlorpromazine) and atypical (risperidone) neuroleptics. Neuropsychological assessment comprised of executive, memory and psychomotor testing. After a nine week trial, having been neuropsychologically assessed at four time points, no differentiation in functioning could be observed between the groups on high doses of standard and atypical neuroleptics and a control group on a standard medication regime. All the trial groups showed neuropsychological impairment at baseline on many of the tests, of the three domains of functioning, which had comparative normative data. None of the treatment regimes was more beneficial than another in terms of symptom improvement, and amelioration of side effects, at the end of the nine week trial. Within subject analyses showed no significant improvement, over time, on any of the drug regimes. It would appear that a sub group of chronic schizophrenic patients exist that are resistant not only to standard neuroleptic medication at high doses, but also new atypical neuroleptics with different pharmacological action. It has long been realised that a sub group of up to 20% of schizophrenic patients will derive little or no benefit from neuroleptic

medication (Davis et al., 1980). The patients in this study might be representative of such a sub population. However, some studies would indicate that patients resistant to standard, though potent, medication, such as haloperidol, do show significant symptomatic improvement with the atypical neuroleptic clozapine (Kane et al., 1988). Although risperidone has been seen as clinically more beneficial over haloperidol and placebo, in terms of symptom amelioration and reduced side effects with heterogeneous groups of patients (Marder and Meibach, 1994), the present study would not support its use specifically with treatment resistant patients as it appears to provide little clinical advantage over more standard, and less expensive, neuroleptics. Despite this, in the Marder and Meibach (1994) multicentre trial of risperidone, clinical advantage was seen at mid range doses. In the present study symptom comparison was recorded between low dose standard neuroleptic status and optimum doses of the atypical drug. Further research may, therefore, need to concentrate on finding the optimal dose for individual patients by careful titration of the drug and close monitoring of symptom levels, with increasing dose, with treatment resistant patients.

Although clozapine appears to be the best candidate, at present, for drug therapy with treatment resistant patients, research has shown that neuropsychological improvement dose not covary with clinical improvement with the drug (Goldberg et al., 1993). This study did not specifically involve treatment resistant patients. The authors suggested that, as their sample showed impaired neuropsychological functioning at baseline, neuropsychological dysfunction would appear to constitute an abiding core feature of

schizophrenic illness, in the chronic state, and may account for much of the chronic social and vocational disabilities characteristic of chronic schizophrenia. Such a conclusion ought to make clinicians pause and reassess whether medication regimes by themselves can be expected to produce benefits, in everyday functioning, needed to improve the quality of an individual's life over symptomatic improvement. The present results indicate that a sub group of patients exists that is treatment resistant to the majority of contemporary drug therapies. This would imply, on a biological level, that the dysfunctional brain systems putatively underlying symptomatic expression are either more complex than the integration of dopamine and serotinergic systems presently thought as culpable, or that these systems are so damaged that, even at high doses, the available drugs are ineffective. In the later case it would be of more benefit to treat such patients as needing, at least in addition to maintenance medication, neurorehabilitation services to focus on the social and vocational aspects of their illness, to address the abiding fundamental neuropsychological problems characteristic of this type of patient. Such a strategy would need to assess which neuropsychological functions are specifically related to the everyday functional deficits associated with treatment resistance in order to tailor appropriate neurorehabilitation therapies. In the final chapter of this thesis these issues were addressed in an assessment of the neuropsychological correlates of poor outcome in schizophrenia.

7.5 Poor outcome in schizophrenia and neuropsychology

The neuropsychological analysis of good versus poor outcome in schizophrenia provided increased support for a fundamental episodic memory impairment characterising poor outcome. Executive impairment, characteristic of poor outcome, was also observed in terms of sustained attention, inhibition of inappropriate responding and semantic word fluency. However, these executive impairments became non significant after accounting for the significantly poorer educational backgrounds of the poor outcome patients. The memory impairment was robust despite education. This poverty of educational experience was seen as a product of an insidious disease process, of early onset, as the two groups came from similar socio-economic groups. This pattern of illness onset has been singled out as a predictor of poor prognosis previously (Lieberman and Sobel, 1993). The patients were dichotomised by clinical and social functioning levels. Therefore, the neuropsychological functioning of a group of patients, which had been categorised as poor outcome due to persistent symptoms (mainly positive) and poor social functioning, was found to be characterised by poor episodic memory. The theoretical associations between memory and social functioning has been addressed above (7.3) and appears to be especially related to overall poor outcome in schizophrenia, possibly due to a neurodevelopmental disorder. We, therefore, may be beginning to realise what underlying neuropsychological impairments are associated with the social dysfunction characteristic of schizophrenia, and more relevantly, of poor outcome.

It has been noted that contemporary drug regimes may only have limited benefit for treatment resistant or poor outcome schizophrenic patients (7.4). The present results should provide a basis for casting the therapeutic net further than concentrating on medication issues with these patients, who display stubborn and fundamental neuropsychological and related social (and vocational) dysfunction. It has already been highlighted that baseline social skills deficits and rate of social skill acquisition are related to the severity of memory impairments in groups of heterogeneous schizophrenic patients (Mueser et al., 1991). Social skills therapies would profit from the realisation that episodic memory functioning is a fundamental impairment in particularly poor outcome schizophrenia. There would appear to be a need to construct therapies that account for these core deficits. More emphasis on socially based therapies seems to be necessitated in a programme of therapy, involving medication, for treatment resistant patients. These patients require, by definition, greater therapeutic input to increase their quality of life, in terms of social and vocational functioning, than an overreliance on medication regimes, sufficient for more treatment responsive patients. The present neuropsychological findings ought to help create rehabilitation therapies that meet with more success, being derived from scientifically based neuropsychological research. Alternatively, as the charateristic fundamental cognitive deficits, of treatment resistant patients, are being understood, therapies might concentrate rather on the cognitive strengths of these patients i.e. those areas of functioning relatively less damaged than memory functioning, to enhance the possibility of therapeutic success.

7.6 Conclusions

The use of neuropsychological assessment on the analysis of symptoms, medication and outcome in schizophrenia highlighted three important features. Firstly, that episodic memory impairment appears to be directly related to much of the social difficulties characteristic of the deficit symptoms of schizophrenia, but especially with regard to poor outcome. Secondly, this type of assessment appears to be limited in an explanation of the direct cognitive processes responsible for abnormal experiential behaviour. However, the patterns of neuropsychological dysfunction and emergent sub syndromes of schizophrenia enabled reasonable speculation as to the genesis of such symptoms, highlighting a wider appreciation of personal and environmental issues, that interact with cognitive deficits, in the formation of abnormal beliefs and experiences. Further studies using measures that are theory lead ought to clarify the interaction of these variables in the formation of positive symptomatology. The use of general neuropsychological measures, in the present studies, was exhaustive and focussed on the integration of functioning with respect to schizophrenic symptomatology. However, the specificity of information; personal, environmental and neuropsychological, required to formulate a idiosyncratic model of schizophrenic functioning necessiates less general measures than those derived from general neurological sources. Thirdly, the significant proportion of treatment resistant patients were seen as necessitating more involved service input emphasising social, as well as drug, therapies to account for the fundamental neuropsychological deficits,

particularly of memory, expressed by these type of patients that deprive them of enriching social experiences and maintain a disturbing and alienating illness state.

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APPENDIX 1

MISSING NEUROPSYCHOLOGICAL TEST DATA FROM THE STUDY OF HIGH CPZ (1) VERSUS RISPERIDONE (2) VERSUS CONTROL (3) GROUPS OF TREATMENT RESISTANT SCHIZOPHRENIC PATIENTS.

Research No.	Group	Missing Data
019	1	Refused DMTS day 7. Refused all testing day 21.
103	1	RT aborted due to failure; no idea how to attempt Tower of London day 7.
036	1	DNA for all testing day 21 (no psychiatric ratings on day 21 for same reason).
105	2	No NART (day 7) or Stroop (days 7&63) as S refuses to speak.
016	2	Refused all CANTAB day 21. No testing after day 21 as S withdrew from the study.
033	2	No Stroop, DMTS, Tower of London days 7&63 as S is colour blind. Refused all tesing days 21&42.
108	2	Refused all CANTAB day 21.
030	2	Refused all testing days 42&63.
023	2	Refused all testing day 63.
101	3	Unable to attempt Tower of London days 7&63.
012	3	Refused all testing day 21.
005	3	Unable to attempt Tower of London day 7. Refused all testing days 21&42 (no psychiatric ratings for the same reason).
027	3	Refused all testing days 21&42 (no psychiatric ratings day 42 for the same reason).
032	3	Tower of London aborted after three inital problems failed day 7.
107	3	Refused all CANTAB day 21.
039	3	Refused all testing day 63.
040	3	Refused digit span, digit symbol substitution test, verbal fluency and Rivermead Behavioural Memory Test day 21. Refused all testing days 42&63.

APPENDIX 2

A SYSTEMATIC CATEGORISATION OF LEVELS OF TREATMENT RESPONSE IN SCHIZOPHRENIA

Taken from:-

May P.R.A., Dencker S.J., Hubbard J.W., Midha K.K. and Liberman R.P. (1988). A systematic approach to treatment resistance in schizophrenic disorders. In: Treatment Resistance in Schizophrenia, pages 22-33 Editors - Dencker S.J. and Kulhanek F. Published by Vieweg, Braunschweig/Wiesbaden.

Degree of Resistance

Treatment Resistance is not an all-or-nothing, present or absent phenomenon, it is a matter of degrees of resistance. Six levels or stages of treatment resistance may be defined; these are arbitrarily based on the time taken to respond to what would be considered a "good" level of treatment by current standards, which is "appropriate" to the particular stage of the disorder and to that of treatment - i.e. pharmacotherapy, psychosocial treatment, and psychotherapeutic management, suitably adjusted to individual needs.

Level 1 (excellent responders): total remission within a week, whatever treatment is given.

Level 2 (very good responders): patients who respond well within one month when given antipsychotic medication in usually recommended dosages. There is "clinical remission", in that they are able to return to the same social situation as before the illness, with little, if any residual scarring.

Level 3 (good responders): patients who show major reduction of symptoms within a month, but still have definite signs of residual schizophrenic disorder, such as autistic thinking or behaviour, or disturbed ego identity. There is "social remission", in that they are able to return to their earlier social existence, but show some (though not great) reduced ability to study or to work.

Level 4 (fair responders): patients whose condition heals slowly and incompletely; besides antipsychotic medication, they also need a structured rehabilitation programme, after a long or fairly long period of hospital stay. There is no clinical remission and only partial social remission. They can leave the hospital, but continued support and/or rehabilitation are required if they are to survive in society.

Level 5 (poor responders): patients who have been given antipsychotic medication in conventional doses for a minimum of six months, as well as standard rehabilitation and non-drug treatment programmes at a defined supportive level, but whose psychotic symptoms or disturbed behaviour do not remit sufficiently to permit entry into ordinary group rehabilitation programmes, or where treatment has had to be abandoned because of toxicity or other unwanted effects. The severity of their residual symptoms is such that these patients will remain for a long while to hospital or in some alternative form of caring milieu, such as a hostel or family care. There is neither social nor clinical remission.

Level 6 (severe treatment resistance): patients who show a failure to respond to any useful extent after six months' hospital treatment including antipsychotic drugs given with measured and presumably adequate plasma levels, and accompanied by an intensive level of psychosocial intervention. They remain in hospital or equivalent care.

In hospital practice, there is a concern particularly with level 5 and 6 of treatment resistance.

APPENDIX 3

Trial number	Medication code number	Patient's Initials

POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) RATING FORM

		ABS	MIN	MILD	MOD	MOD SEV	SEV	EXT
POSITIVE SCALE								
P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual Disorganisation	1	2	3	4	5	6	7
P3	Hallucinatory Behaviour	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/Persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7
NEGATIVE SCALE								
N1	Blunted Affect	1	2	3	4	5	6	7
N2	Emotional Withdrawal	1	2	3	4	5	6	7
N3	Poor Rapport	1	2	3	4	5	6	7
N4	Passive/Apathetic Social Withdrawal	1	2	3	4	5	6	7
N5	Difficulty in Abstract Thinking	1	2	3	4	5	6	7
N6	Lack of Spontaneity and Flow of Conversation	1	2	3	4	5	6	7
N7	Stereotyped Thinking	1	2	3	4	5	6	7

APPENDIX 1

GOOD 4:1:6

0-2

COOPERS SOCIAL OUTCOME SCALE

1. ECONOMIC STATUS

(a) Supporting self entirely and possibly others in household, during most of previous 12 months - Score 2

(b) Working sometimes but partly dependent financially on relatives or some state assistance-Score 1.

(c) Unemployed and completely dependent financially.Includes inpatients.-Score 0

2. SOCIAL LIABILITY

(a) Behaving normally, restored to pre-morbid personality or only mild residual personality changes -Score 2

(b) Suffering persistent or recurrent psychotic symptoms, but not grossly disturbed in behaviour and able to maintain interpersonal relationships to a reasonable degree-Score 1

(c) Showing gross behaviour disturbances due to psychotic symptoms,and unable to maintain interpersonal relationships-Score 0

3. SELF-CARE

(a) Normal standard, no help needed regarding personal appearance,dress,toilet or use of money -Score 2

(b) Slovenly,apathetic or withdrawn,requiring some supervision and occasional help with appearance,toilet or use of money-Score 1

(c) Incapable of self-care through persistent mental illness, and needing considerable help with dress, toilet and money -Score 0

4. TOTAL SOCIAL ADJUSTMENT SCORE

Total of 1. 2. 3.-Varying from 0 to 6-
Total of 5 or 6 - Good
Total of 3 or 4 - Fair
Total of 0 or 1 or 2 - Poor.

Cross-Sectional Outcome Scale (McGlashan 1984)

Item 1. Duration of hospitalization in the past year for psychiatric disorder

4. Not in hospital in past year (exclude hospitalization at time of first interview if less than one month following first interview)
3. Hospitalized less than three months in past year.
2. Hospitalized three to six months in past year.
1. Hospitalized over six months, up to nine months in past year.
0. Hospitalized more than nine months in the past year.

Item 2. Social contacts (The approximate number of times the patient has met with friends outside the family over the last year.)

4. Meets with friends on average at least once a week.
3. Meets with friends every two weeks.
2. Meets with friends about once a month.
1. Meets only at work or at school.
0. Does not meet with friends .

Item 3. Usefully employed (include work as housewife, student. Exclude time in hospital.)

4. Full-time: >40 hr/week
3. Part-time: >20 hr/week
2. Part-time: <20hr/week
1. Unemployed but capable of working.
0. Receiving assistance and not capable of working.

Item 4. Psychopathology (which *in the past month* best describes the patients experience in terms of anxiety, depression, or other signs and symptoms of emotional tension).

4. No signs or symptoms.
3. Slight signs and symptoms most of the time, or moderate signs and symptoms on rare occasions.
2. Moderate signs and symptoms some of the time.
1. Severe signs and symptoms some of the time or moderate signs and symptoms continuously.
0. Continuous and severe signs and symptoms.

Item 5. Global Functioning. (Rate the patient's overall level of functioning in the past year.)

4. No impairment.
3. Some, but not much, impairment.
2. Moderate impairment.
1. A lot of impairment.
0. impairment, Severe

APPENDIX 6.

Total Follow-up Period Outcome Scale (McGlashan 1984)

Item 1. Duration of hospitalization for psychiatric disorder (inc. day hospitals and halfway houses) since first diagnosis

4. No time (or less than 5% of the time)
3. About 25% of the time.
2. About 50% of the time.
1. About 75% of the time.
0. Just about all the time.

Item 2. Social contacts (Check the number of times the patient currently meets with friends outside the family)

4. Meets with friends at least once a week.
3. Meets with friends once every two weeks.
2. Meets with friends about once a month.
1. Meets only at work or school.
0. Does not meet with friends .

Item 3. Employment (employment means working for pay, pursuing studies as a student, caring for a household and raising children or engaging in volunteer work.)

4. Just about all the time.
3. About 75% of the time.
2. About 50% of the time.
1. About 25% of the time.
0. No useful work.

Item 4. Psychopathology (the percentage of time since discharge the patient has experienced anxiety, dpression, or symptoms of emotional tension that were experienced before first diagnosis.

4. Seldom or not at all.
3. About 25% of the time.
2. About 50% of the time.
1. About 75% of the time.
0. All the time.

Item 5. Global Functioning (Take as "normal" someone fully employed, experiencing no symptoms or need for treatment, and engaged meaningfully in family and social relationships; compared with the "normal", rate the patient's overall level of functioning since first diagnosis.)

4. Normal.
3. About 75% of normal.
2. About 50% of normal.
1. About 25% of normal.
0. No period of normal function.